STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 180648

TO: David Lukton
Location: rem/3B75/3C18
Art Unit: 1654
March 15, 2006

Case Serial Number: 10/606422

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

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ACCESS DB # 180648
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SEARCH REQUEST FORM
(STIC)

Requestor's Name: David Lukton Examiner number: 71263 Date: 2/27/06 MG

Art Unit: 1654 Phone number: 571-272-0952 Serial Number: 10-606422

Mail Box: 3-C-18 Examiner Rm: 3-B-75 Results format: paper

* * * * * * * *

Title: SUBSTITUTED HETEROCYCLIC ACYL-TRIPEPTIDES USEFUL AS THROMBIN RECEPTOR MODULATORS

Applicants: MCCOMSEY, DAVID F.; MARYANOFF, BRUCE E.; HAWKINS, MICHAEL J.

Earliest priority date: 12/14/98

* * * * * * * *

Applicants are claiming compounds of the following formula:

$Y\text{-}X\text{-}A^1\text{-}A^2\text{-}A^3\text{-}Z$

Y = aryl, substituted aryl, heteroaryl, or heterocycloalkyl, but with the proviso that **Y is not** pyrrolidinyl or phenyl or 2-aminophenyl;

X = -CO-, -C=S- or $-SO_2-$

A^1 is an amino acid residue selected from Leu, Ile, Arg, Lys, Phe, Tyr & Trp

A^2 is lysine or arginine;

A^3 is an amino acid residue selected from Phe, Tyr, Trp, Leu, Ile, Asn, Gln, Arg, Lys;

Z is $-NH_2$, NH-R or Arg-NH_2

wherein R is alkyl or benzyl or phenethyl

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STAFF USE ONLY

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Searcher Phone #: _____

Searcher Location: _____

Date Searcher Picked Up: _____

Date Completed: _____

Searcher Prep & Review Time: _____

Online Time: _____

Type of Search

_____ NA Sequence (#)

_____ AA Sequence (#)

_____ Structure (#)

_____ Bibliographic

_____ Litigation

_____ Fulltext

_____ Other

Vendors and cost where applicable

_____ STN _____ Dialog

_____ Questel/Orbit _____ Lexis/Nexis

_____ Westlaw _____ WWW/Internet

____ In-house sequence systems

__ Commercial ___ Oligomer ____ Score/Length

__ Interference ___ SPDI ____ Encode/Transl

_____ Other (specify)

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     Property values tagged with IC are from the ZIC/VINITI data file
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     STRUCTURE FILE UPDATES:   14 MAR 2006  HIGHEST RN 876856-38-1
     DICTIONARY FILE UPDATES:  14 MAR 2006  HIGHEST RN 876856-38-1

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

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* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

FILE HCAPLUS

FILE COVERS 1907 - 15 Mar 2006 VOL 144 ISS 12
FILE LAST UPDATED: 14 Mar 2006 (20060314/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE COVERS 1907 - 15 Mar 2006  VOL 144 ISS 12
FILE LAST UPDATED: 14 Mar 2006  (20060314/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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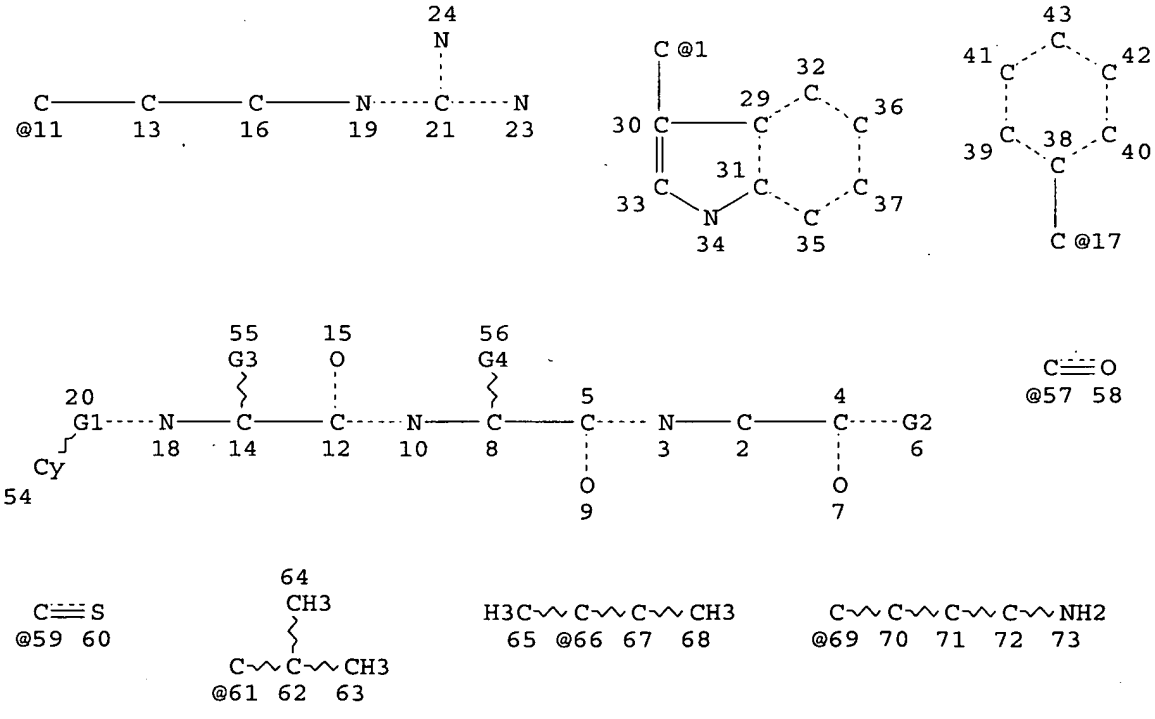

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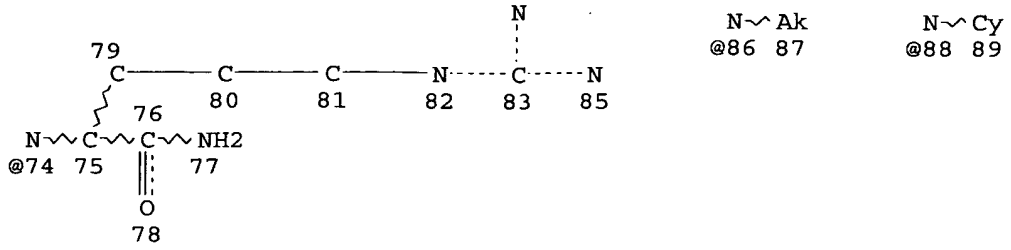

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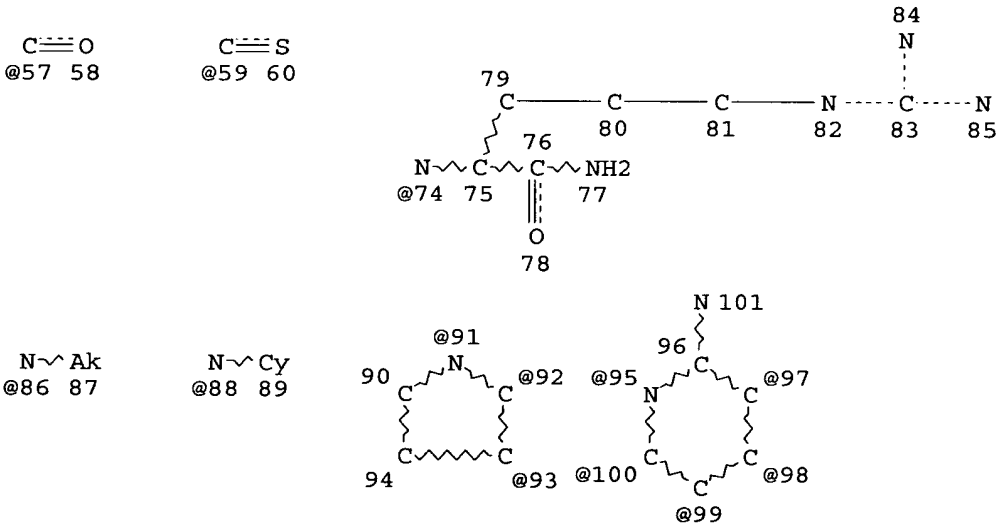

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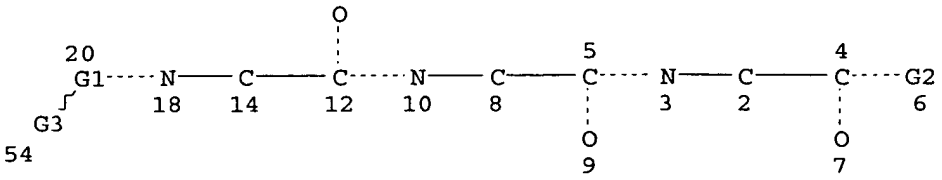

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L11 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:539953 HCAPLUS
DOCUMENT NUMBER: 141:106734
TITLE: Preparation of peptide factor Xa inhibitors as antithrombotics.
INVENTOR(S): Al-Obeidi, Fahad; Lebl, Michal; Ostrem, James A.; Safar, Pavel; Stierandova, Alena; Strop, Peter; Walser, Armin
PATENT ASSIGNEE(S): Aventis Pharmaceuticals Inc., USA
SOURCE: U.S., 32 pp., Cont.-in-part of U.S. 5,849,510. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 6759384	B1	20040706	US 1998-211715		19981214
EP 1384725	A2	20040128	EP 2003-21617		19950425
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
US 5849510	A	19981215	US 1997-947794		19971008 <--
PRIORITY APPLN. INFO.:			US 1994-233054	B2	19940426
			US 1995-428404	B1	19950425
			US 1997-947794	A2	19971008
			EP 1995-917736	A3	19950425

AB The invention provides compds. A1-A2-(A3)m-B [m = 0, 1; A1 = R1-R2-R3; A2 = R4-R5-R6; A3 = R7-R8-R9; R1 = (substituted) 1-20 amino acid residues, R11CO, R11R12X; X = N, CH, NCO; R11, R12 = H, alkyl, acyl, aryl, aralkyl,

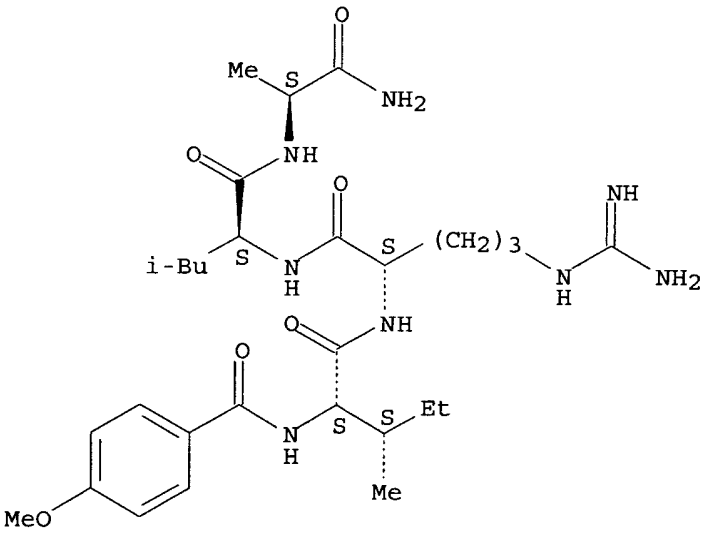
protecting group; R2 = CR99R100; R99, R100 = H, (substituted) alkyl, aralkyl, heteroaralkyl, heteroaryl; R3 = CO, CH2, CHR99CO, etc.; R4 = CH2, imino; R5 = CR201R202; R201, R202 = H, (substituted) alkyl, aryl, aralkyl; R6 = CO, CH2, CHR99CO; R7 = (substituted) R4; R8 = CR210R211; R210, R211 = H, (substituted) alkyl, alkylaryl, heterocyclyl; R9 = CO, CH2, CHR99CO; B = (substituted) 1-20 amino acid residues, amino, OH, alkoxy, acyloxy, etc.; with provisos] which specifically inhibit factor Xa activity. A compound of the invention is characterized, in part, in that it exhibits a specific inhibition of factor Xa activity with a Ki ≤ 100 μM, preferably ≤ 2 nM, and does not substantially inhibit the activity of other proteases involved in the coagulation cascade. Thus, Ac-Tyr-Chg-Arg-NH2 (Chg = cyclohexylglycyl) inhibited coagulation in human plasma with EC50 = 2.5 μM.

IT **718644-56-5P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptide factor Xa inhibitors as antithrombotics)

RN 718644-56-5 HCAPLUS

CN L-Alaninamide, N-(4-methoxybenzoyl)-L-isoleucyl-L-arginyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1998:300866 HCAPLUS

DOCUMENT NUMBER: 129:4872

TITLE: Preparation of targetable diagnostic and therapeutic gas-containing or gas-generating ultrasound contrast agents

INVENTOR(S): Klaveness, Jo; Rongved, Pal; Hogset, Anders; Tolleshaug, Helge; Naevestad, Anne; et al.

PATENT ASSIGNEE(S): Marsden, John Christopher, UK; Nycomed Imaging AS

SOURCE: PCT Int. Appl., 205 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9818501	A2	19980507	WO 1997-GB2954	19971028 <--
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RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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AU 733495	B2	20010517		
BR 9712683	A	19991019	BR 1997-12683	19971028
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EP 973552	B1	20060301		
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JP 2001503407	T2	20010313	JP 1998-520187	19971028
US 6331289	B1	20011218	US 1997-959206	19971028
EP 1442751	A1	20040804	EP 2004-7226	19980424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
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NO 9901889	A	19990628	NO 1999-1889	19990421
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US 2002102217	A1	20020801	US 2001-925715	20010810
US 6680047	B2	20040120		
CN 1440816	A	20030910	CN 2002-160420	20021230
US 2005002865	A1	20050106	US 2003-734730	20031215

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GB 1997-11837	A	19970606
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US 1997-49263P	P	19970607
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US 1997-959206	A	19971028
WO 1997-GB2954	W	19971028
EP 1998-917461	A3	19980424
US 2001-925715	A1	20010810

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, comprising a suspension in an aqueous carrier liquid

of a reporter comprising gas-containing or gas-generated material, in which the reporter is coupled or linked to one or more non-bioactive vectors. Thus, a mixture of phosphatidylserine, phosphatidylcholine, and biotinamidocaproate-PEG3400-L-Ala-cholesterol (preparation given) was dispersed in 5% propylene glycol-water, flushed with perfluorobutane, and sonicated to give gas-filled encapsulated microbubbles.

IT **207302-67-8P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of targetable diagnostic and therapeutic gas-containing or gas-generating ultrasound contrast agents linked to non-bioactive vectors)

RN 207302-67-8 HCAPLUS

CN L-Cysteine, N-[[4-[[4-(dimethylamino)phenyl]azo]phenyl]sulfonyl]-L-tyrosyl-L-arginyl-L-alanyl-L-leucyl-L-valyl-L-α-aspartyl-L-threonyl-L-leucyl-L-lysyl-N6-(L-arginylglycyl-L-α-aspartyl-L-seryl)-L-lysylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

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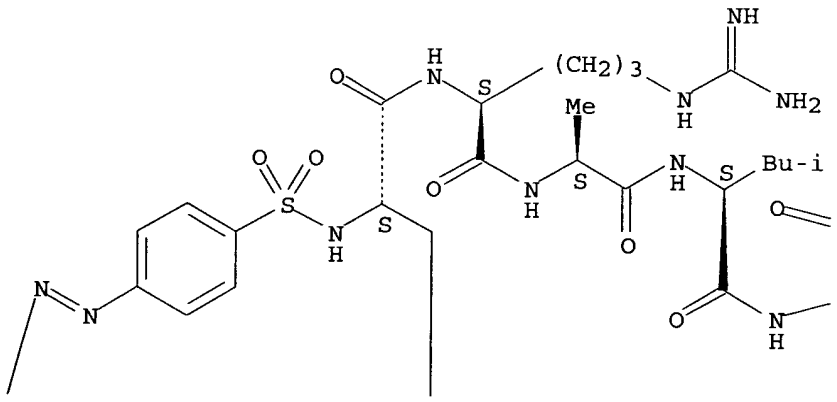

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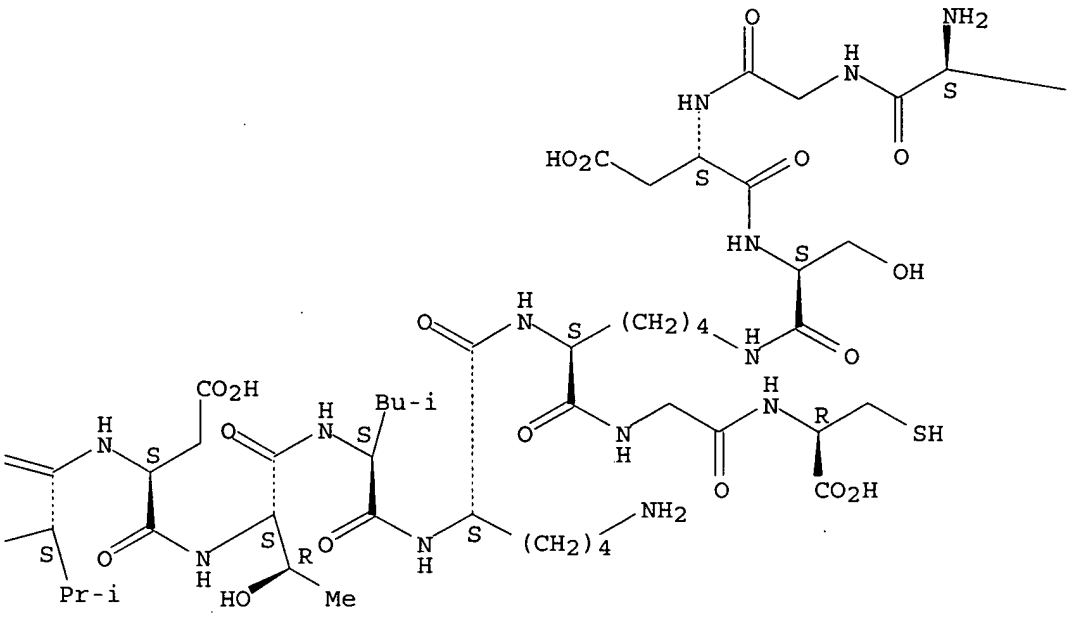

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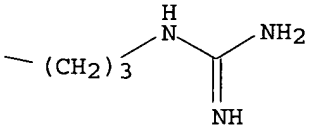

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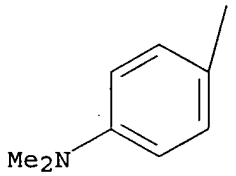

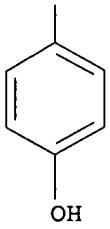

L11 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:300865 HCAPLUS
DOCUMENT NUMBER: 129:4871
TITLE: Preparation of targetable diagnostic and therapeutic gas-containing or gas-generating ultrasound contrast agents
INVENTOR(S): Klaveness, Jo; Rongved, Pal; Hogset, Anders;

	Tolleshaug, Helge; Cuthbertson, Alan; et al.
PATENT ASSIGNEE(S):	Marsden, John Christopher, UK; Nycomed Imaging AS
SOURCE:	PCT Int. Appl., 150 pp.
	CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	9
PATENT INFORMATION:	

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RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
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	US 1997-959206	A 19971028
	WO 1997-GB2953	W 19971028
	EP 1998-917461	A3 19980424
	US 2001-925715	A1 20010810

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, comprising a suspension in an aqueous carrier liquid

of a reporter comprising gas-containing or gas-generated material, in which the reporter is coupled or linked to one or more non-bioactive vectors. Thus, lipopeptide R-Lys(R)-Lys-Arg-Lys-Arg-Trp-Glu-Pro-Pro-Arg-Ala-Arg-Ile-OH (I; R = hexadecanoyl) (preparation given) containing a heparin binding site and
a fibronectin binding site, was prepared by standard solid-phase methods. Microbubbles containing lipopeptide I were tested in vitro for binding to endothelial cells under flow conditions.

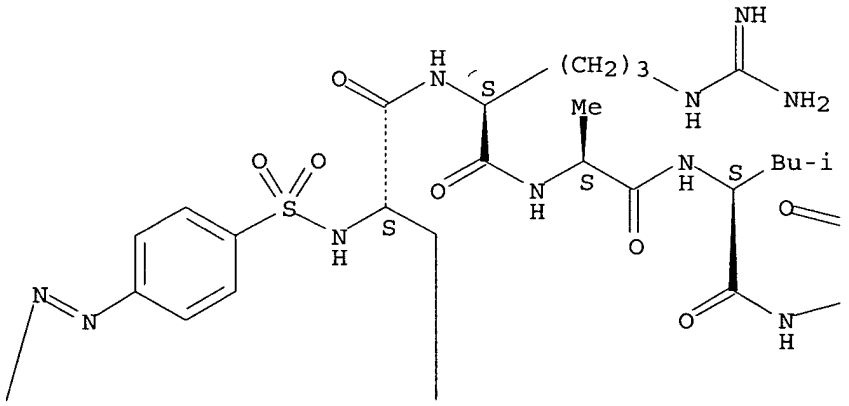
IT **207302-67-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of targetable diagnostic and therapeutic gas-containing or gas-generating ultrasound contrast agents linked to non-bioactive vectors)

RN 207302-67-8 HCAPLUS

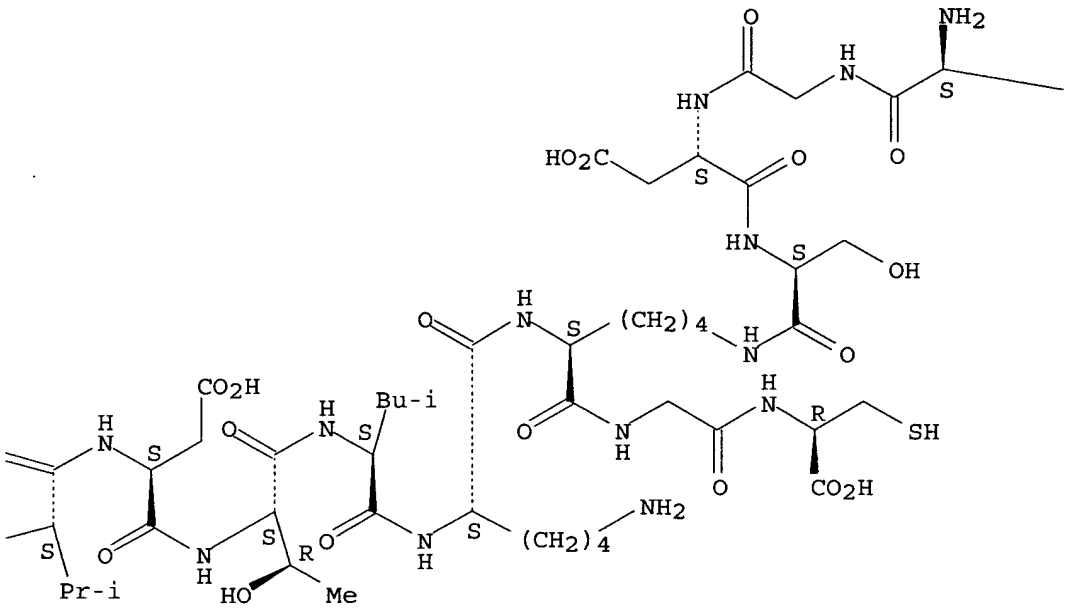
CN L-Cysteine, N-[[4-[[4-(dimethylamino)phenyl]azo]phenyl]sulfonyl]-L-tyrosyl-L-arginyl-L-alanyl-L-leucyl-L-valyl-L-α-aspartyl-L-threonyl-L-leucyl-L-lysyl-N6-(L-arginylglycyl-L-α-aspartyl-L-seryl)-L-lysylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

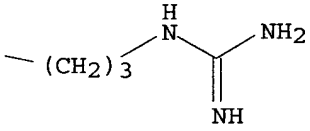
PAGE 1-A



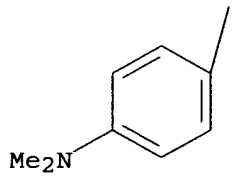
PAGE 1-B

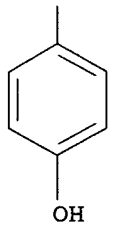


PAGE 1-C



PAGE 2-A





L11 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:248791 HCAPLUS
DOCUMENT NUMBER: 126:327291
TITLE: Design of kallidin-releasing tissue kallikrein inhibitors based on the specificities of the enzyme's binding subsites
AUTHOR(S): Portaro, Fernanda C. V.; Cezari, Maria H. S.; Juliano,

Maria A.; Juliano, Luiz; Walmsley, Adrian R.; Prado, Eline S.
CORPORATE SOURCE: Department Biophysics, Universidade Federal Sao Paulo-Escola Paulista Medicina, Sao Paulo, 04044-020, Brazil
SOURCE: Biochemical Journal (**1997**), 323(1), 161-171
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tissue kallikrein inhibitors were derived by selectively replacing residues in Nα-substituted arginine- or phenylalanine-pNA (where pNA is p-nitroanilide), and in peptide substrates for these enzymes. Phenylacetyl-Arg-pNA was an efficient inhibitor of human tissue kallikrein (Ki 0.4 μM) and was neither a substrate nor an inhibitor of plasma kallikrein. The peptide inhibitors having phenylalanine as the P1 residue behaved as specific inhibitors for kallidin-releasing tissue kallikreins, whereas plasma kallikrein showed high affinity for inhibitors containing (p-nitro)phenylalanine at the same position. The Ki value of the most potent inhibitor developed, Abz-Phe-Arg-Arg-Pro-Arg-EDDnp [where Abz is o-aminobenzoyl and EDDnp is N-(2,4-dinitrophenyl)-ethylenediamine], was 0.08 μM for human tissue kallikrein. Progress curve analyses of the inhibition of human tissue kallikrein by benzoyl-Arg-pNA and phenylacetyl-Phe-Ser-Arg-EDDnp indicated a single-step mechanism for reversible formation of the enzyme-inhibitor complex.

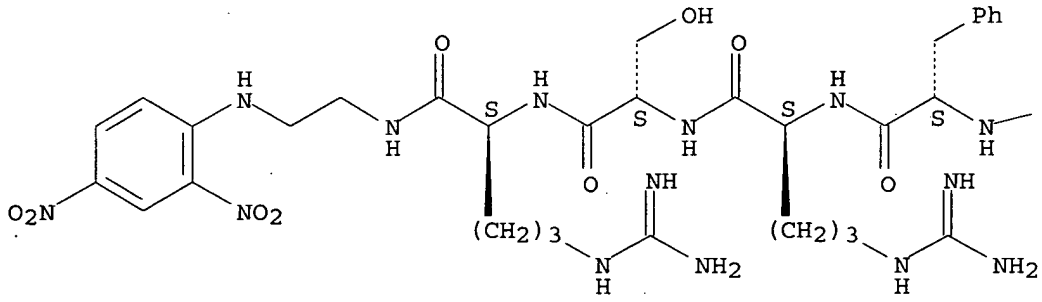
IT **133839-14-2 133839-16-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(design of kallidin-releasing tissue kallikrein inhibitors based on the specificities of the enzyme's binding subsites)

RN 133839-14-2 HCAPLUS

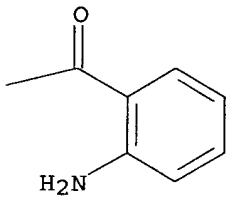
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



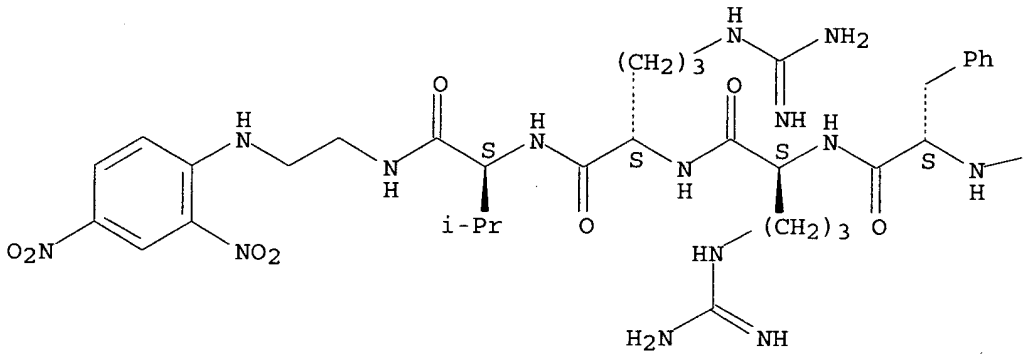
PAGE 1-B



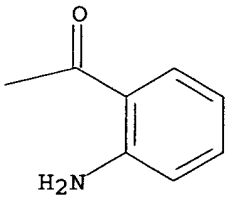
RN 133839-16-4 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-arginyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:155533 HCAPLUS
DOCUMENT NUMBER: 124:212160
TITLE: Monoamine, diamide, thiol-containing metal chelating agents
INVENTOR(S): Mcbride, William; Dean, Richard T.

PATENT ASSIGNEE(S): Diatech, Inc., USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 44
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9533497	A1	19951214	WO 1995-US6914	19950601	<--
W: AU, BR, CA, CN, JP, KR					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2191951	AA	19951214	CA 1995-2191951	19950601	<--
AU 9526944	A1	19960104	AU 1995-26944	19950601	<--
AU 707040	B2	19990701			
BR 9507917	A	19970812	BR 1995-7917	19950601	<--
CN 1158090	A	19970827	CN 1995-194356	19950601	<--
CN 1093424	B	20021030			
EP 804252	A2	19971105	EP 1995-922159	19950601	<--
EP 804252	B1	20030813			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
JP 10501531	T2	19980210	JP 1996-501181	19950601	<--
JP 3727342	B2	20051214			
AT 246939	E	20030815	AT 1995-922159	19950601	
PT 804252	T	20031231	PT 1995-922159	19950601	
ES 2204954	T3	20040501	ES 1995-922159	19950601	
ZA 9504548	A	19960315	ZA 1995-4548	19950602	<--
PRIORITY APPLN. INFO.:			US 1994-253973 A	19940603	
			WO 1995-US6914 W	19950601	

OTHER SOURCE(S): MARPAT 124:212160

AB The invention relates to reagents useful in preparing radiolabeled diagnostic and therapeutic agents (radiopharmaceuticals). Specifically, the invention provides such reagents that are monoamine, diamide, and thiol-containing metal chelators. Methods of making such reagents, and methods of using the radiopharmaceuticals produced therefrom are also provided.

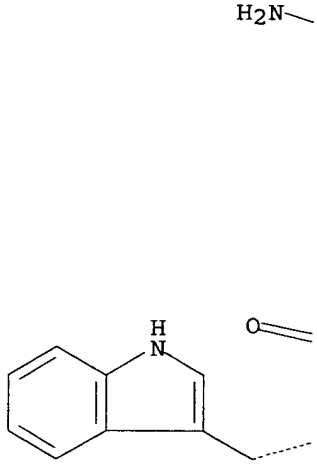
IT **161982-53-2DP**, technetium 99 complexes **174350-41-5DP**, technetium 99 complexes
RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(monoamine, diamide, and thiol-containing metal chelating agents as radiopharmaceuticals)

RN 161982-53-2 HCAPLUS

CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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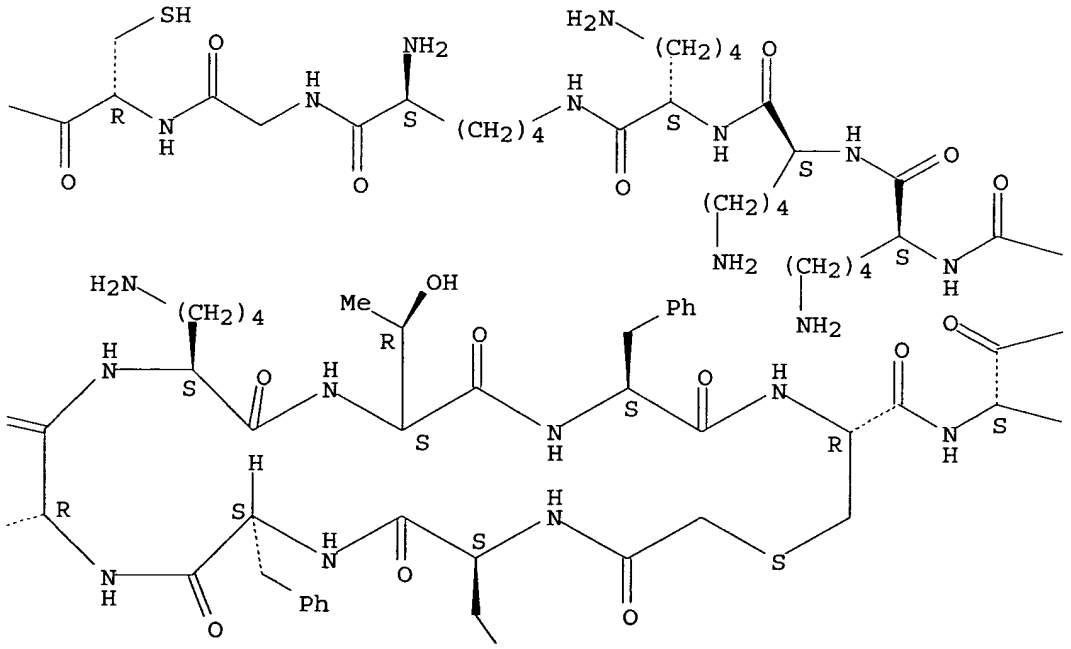

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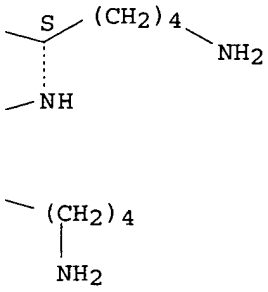
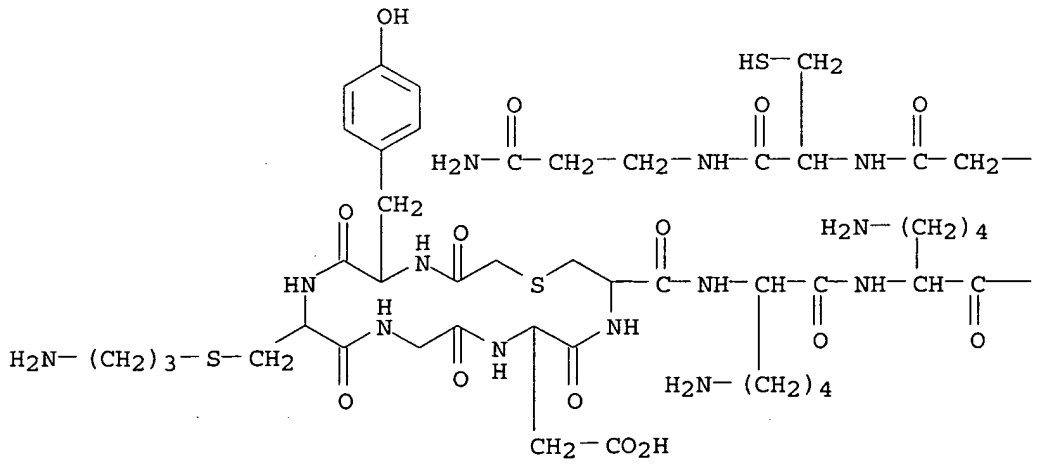


PAGE 2-B

RN 174350-41-5 HCAPLUS
CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

PAGE 1-A



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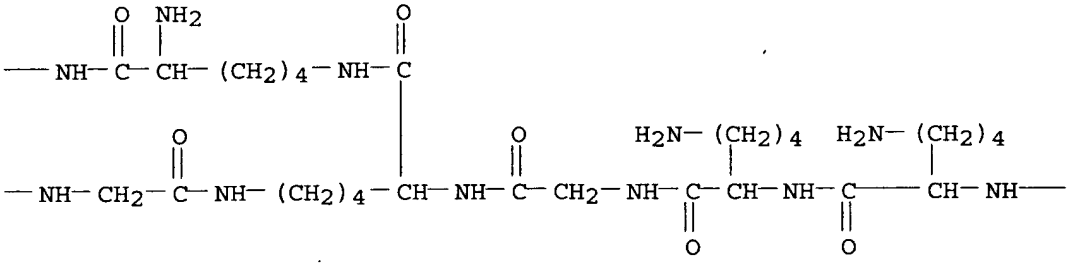

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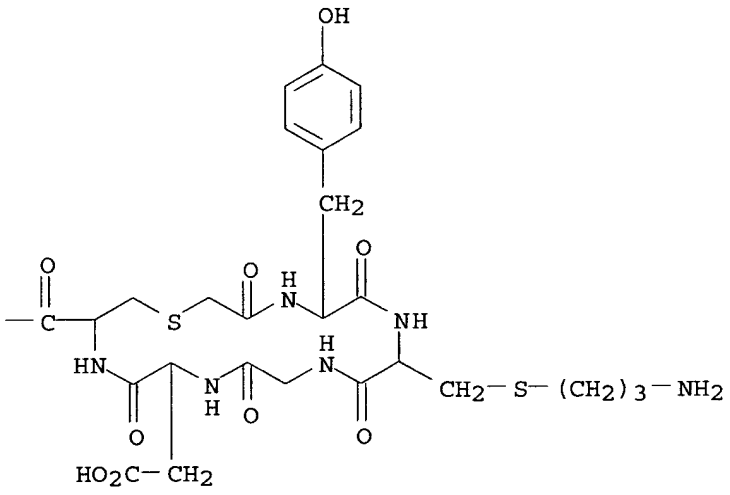


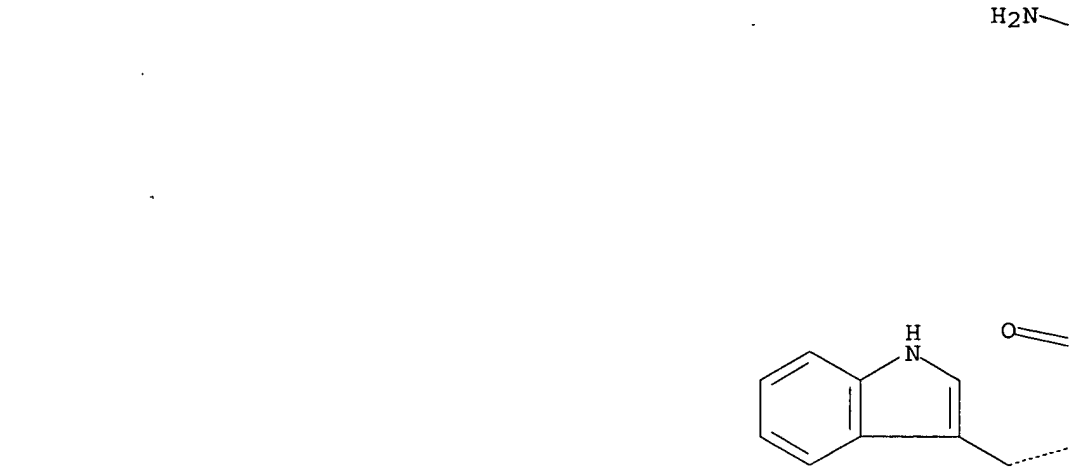
IT **161982-53-2P 174350-41-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(monoamine, diamide, and thiol-containing metal chelating agents as radiopharmaceuticals)

RN 161982-53-2 HCAPLUS

CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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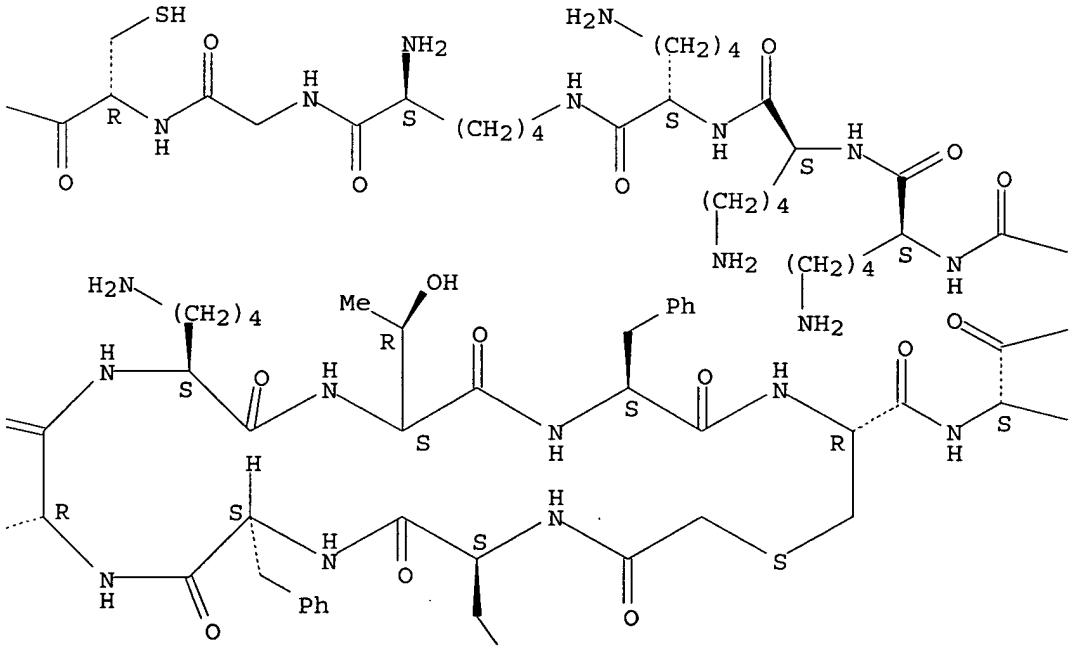

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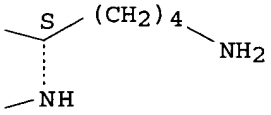
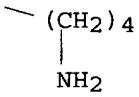
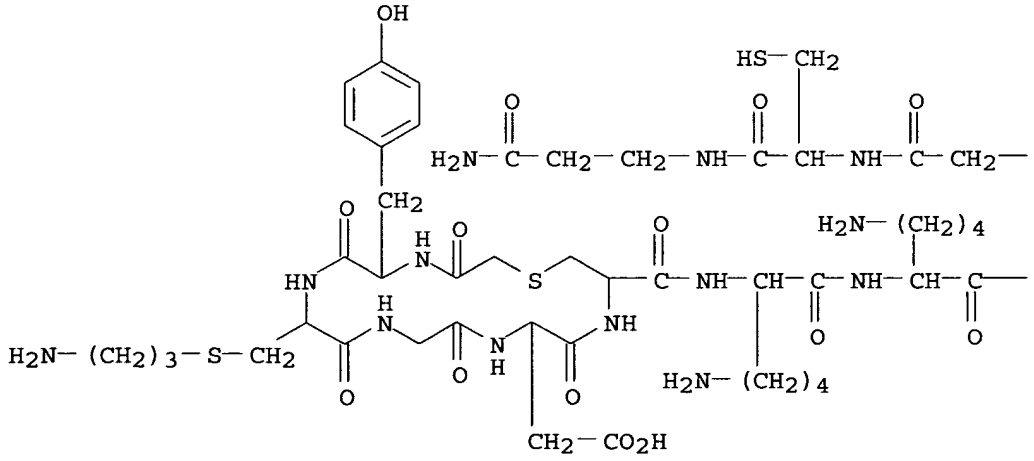




PAGE 2-B

RN 174350-41-5 HCAPLUS
CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-S-(3-aminopropyl)-L-cysteinylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

PAGE 1-A



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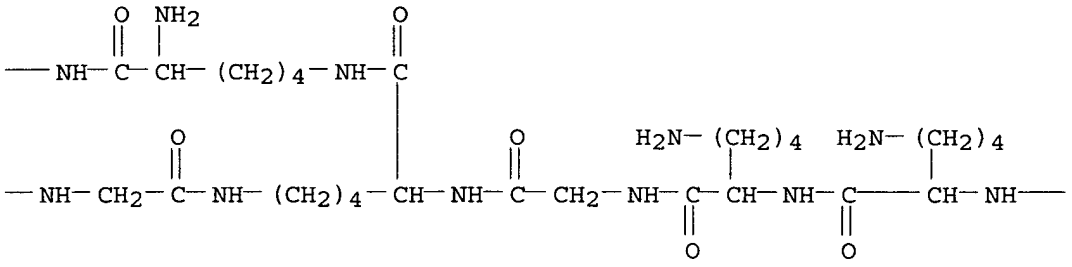

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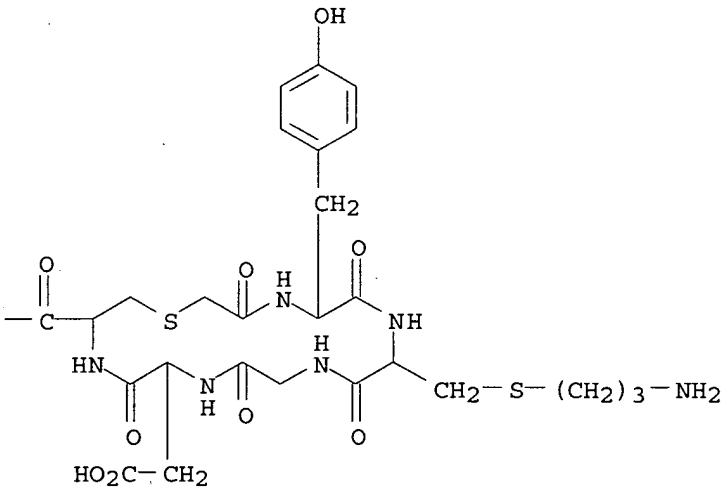


L11 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:465577 HCAPLUS
DOCUMENT NUMBER: 122:234388
TITLE: Radiolabeled somatostatin-derived peptides for imaging and therapeutic uses
INVENTOR(S): Dean, Richard T.; McBride, William; Lister-James, John
PATENT ASSIGNEE(S): Diatech, Inc., USA
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 44
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9500553	A1	19950105	WO 1994-US6274	19940603 <--

W: AU, CA, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

US 6017509	A	20000125	US 1993-92355	19930715	
AU 9470990	A1	19950117	AU 1994-70990	19940603	<--
AU 701083	B2	19990121			
EP 720621	A1	19960710	EP 1994-920076	19940603	<--
EP 720621	B1	20010207			

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, SE

AT 199089	E	20010215	AT 1994-920076	19940603	
CA 2167281	C	20010904	CA 1994-2167281	19940603	
US 6051206	A	20000418	US 1996-592323	19960506	

PRIORITY APPLN. INFO.:

US 1993-92355	A	19930715
US 1991-807062	A2	19911127
WO 1993-US6029	W	19930623
WO 1994-US6274	W	19940603

OTHER SOURCE(S): MARPAT 122:234388

AB Therapeutic reagents and peptides, including radiotherapeutic reagents and peptides, radiodiagnostic reagents and peptides, and methods for producing labeled radiodiagnostic agents, are disclosed. Specifically, the invention relates to cyclic peptide derivs. and analogs of somatostatin, and embodiments of such peptides radiolabeled with a radioisotope, as well as methods and kits for making, radiolabeling, and using such peptides for radiodiagnostic and radiotherapeutic purposes. The invention specifically relates to cyclic peptide derivs. and analogs of somatostatin radiolabeled with technetium-99m and uses thereof as scintigraphic imaging agents. The invention also specifically relates to cyclic peptide derivs. and analogs of somatostatin radiolabeled with cytotoxic radioisotopes (e.g. 186Re, 188Re) for use as radiotherapeutic agents. Methods and kits for making, radiolabeling, and using such peptides diagnostically and therapeutically in a mammalian body are also provided. Data for binding of the analogs to somatostatin receptors is included, as is use in imaging of somatostatin receptor-expressing tumors.

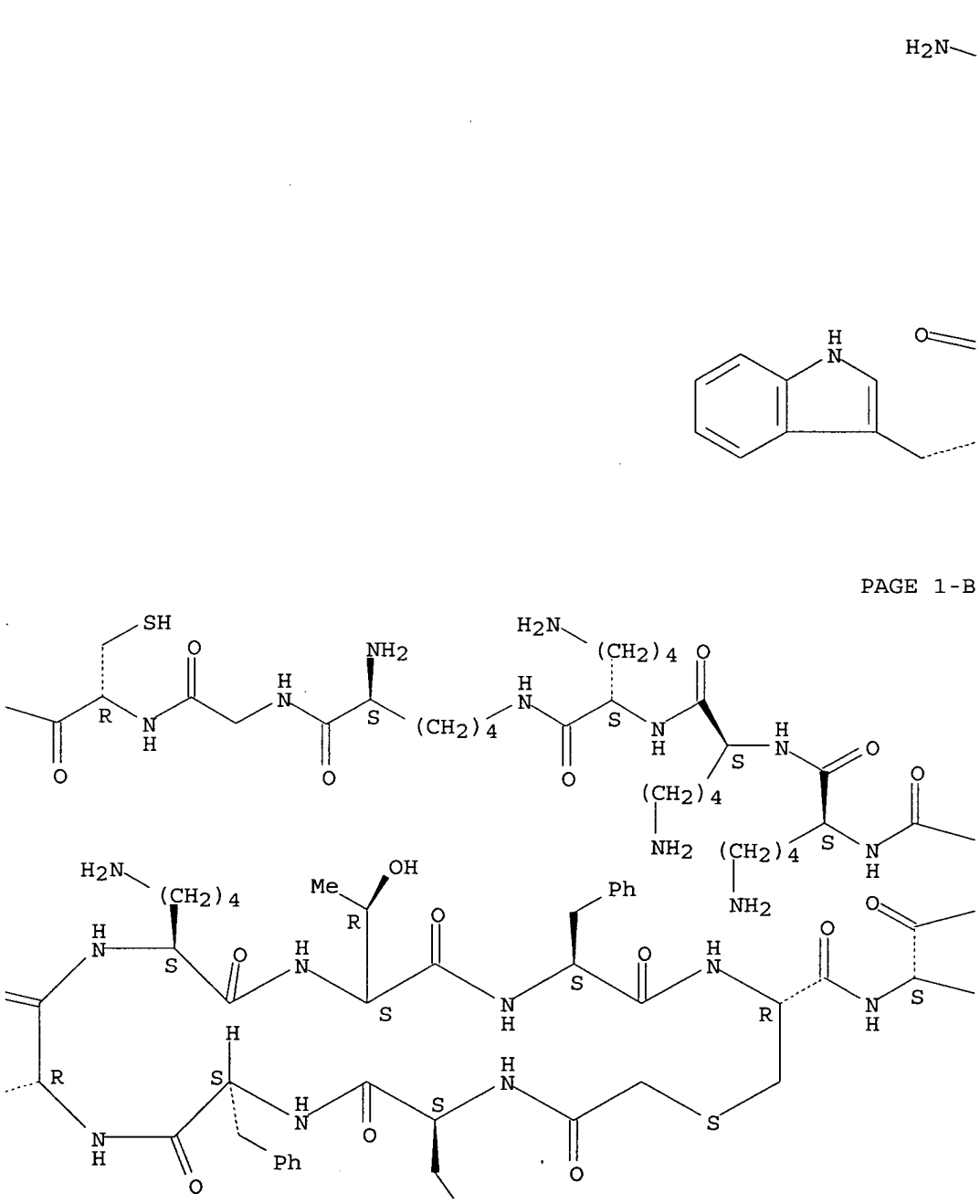
IT **161982-53-2DP**, technetium-99m complexes **161982-53-2P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and use of radiolabeled somatostatin-derived peptides for imaging and therapeutic uses)

RN 161982-53-2 HCAPLUS

CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

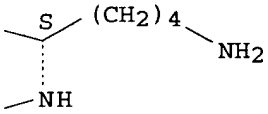
Absolute stereochemistry.

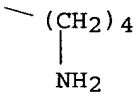
PAGE 1-A



PAGE 1-B

PAGE 1-C



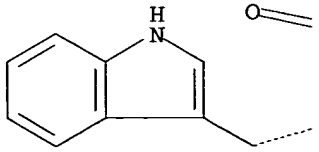


PAGE 2-B

RN 161982-53-2 HCAPLUS
CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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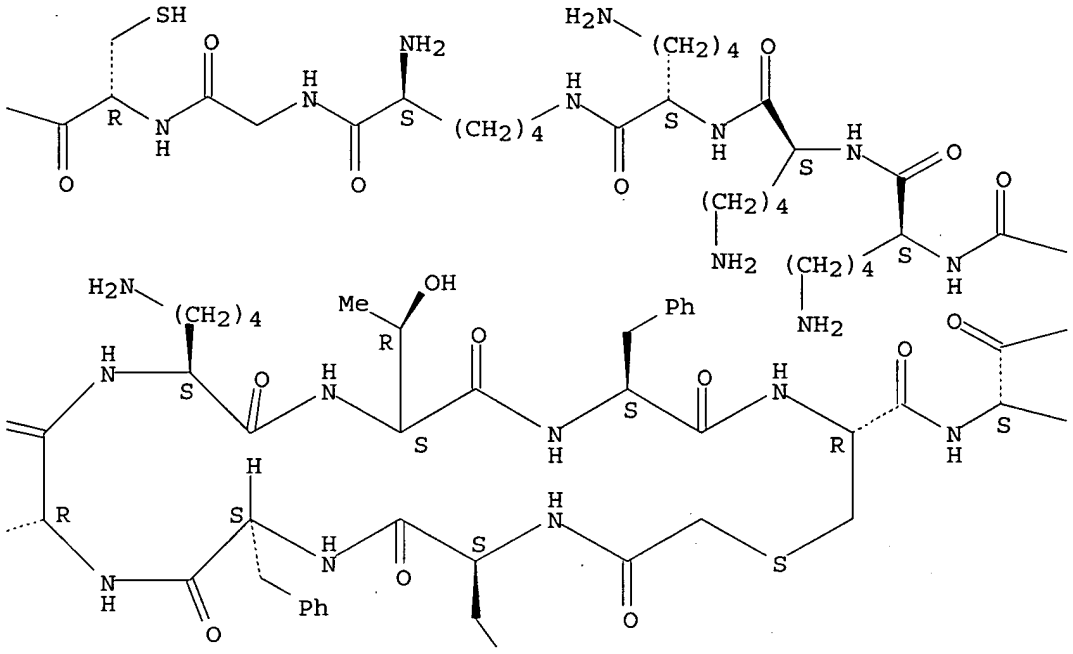

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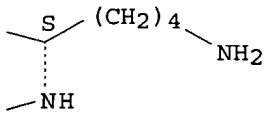
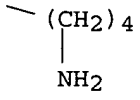




PAGE 2-B

L11 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:381727 HCAPLUS
DOCUMENT NUMBER: 122:285299
TITLE: Determinants of the unusual cleavage specificity of lysyl-bradykinin-releasing kallikreins
AUTHOR(S): Chagas, Jair R.; Portaro, Fernanda C. V.; Hirata, Isaura Y.; Almeida, Paulo C.; Juliano, Maria A.; Julianao, Luiz; Prado, Eline S.
CORPORATE SOURCE: Dep. Biophys., Escola Paulista de Medicina, Sao Paulo, 04044-020, Brazil
SOURCE: Biochemical Journal (**1995**), 306(1), 63-9
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

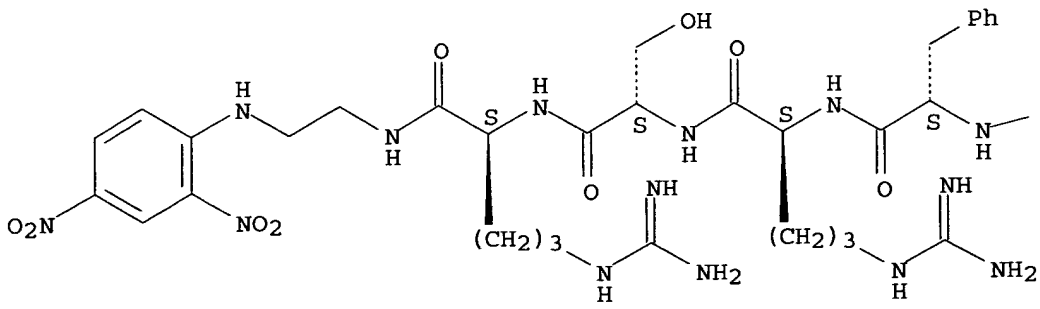
AB Kinetic data for the hydrolysis by human tissue kallikrein of fluorogenic peptides with o-aminobenzoyl-Phe-Arg (Abz-FR) as the acyl group and different leaving groups demonstrate that interactions with the S'1, S'2 and S'3 subsites are important for cleavage efficiency. In addition, studies on the hydrolysis of fluorogenic peptides with the human kininogen sequence spanning the scissile Met-Lys bond [Abz-M-I-S-L-M-K-R-P-N-(2,4-dinitrophenyl)ethylenediamine] and analogs with different residues at positions P'1, P'2 and P'3 showed that (a) the presence of a proline residue at P'3 and the interactions with the tissue kallikrein-binding sites S2 to S'2 are determinants of Met-Lys bond cleavage and (b) residues P3, P4 and/or P5 are important for cleavage efficiency. The substitution of phenylalanine for methionine or arginine in substrates with scissile Met-Lys or Arg-Xaa bonds demonstrated that lysyl-bradykinin-releasing tissue kallikreins also have a primary specificity for phenylalanine. The replacement of arginine by phenylalanine in (D)P-F-R-p-nitroanilide (pNA) produced an efficient and specific chromogenic substrate (D)P-F-F-pNA, for the lysyl-bradykinin-releasing tissue kallikreins as it is resistant to plasma kallikrein and other arginine hydrolases.

IT **133839-14-2 133839-15-3 133839-16-4**
162851-74-3 162851-78-7
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(determinants of unusual cleavage specificity of lysyl-bradykinin-releasing kallikreins)

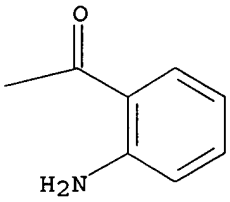
RN 133839-14-2 HCAPLUS
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



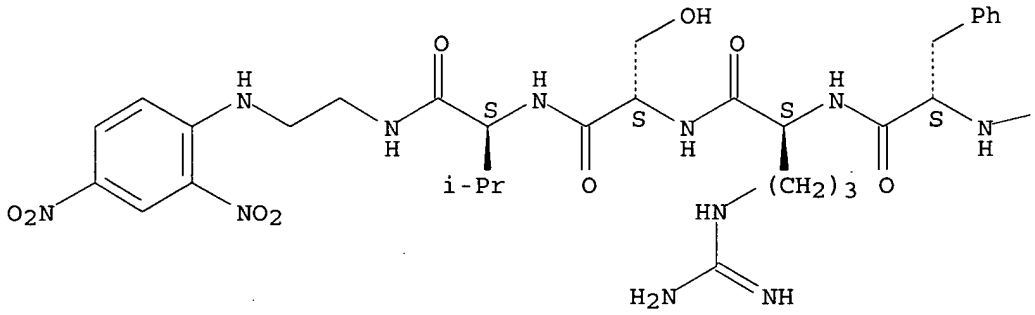
PAGE 1-B



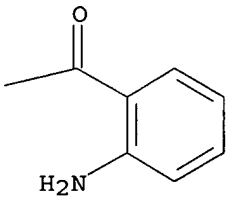
RN 133839-15-3 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



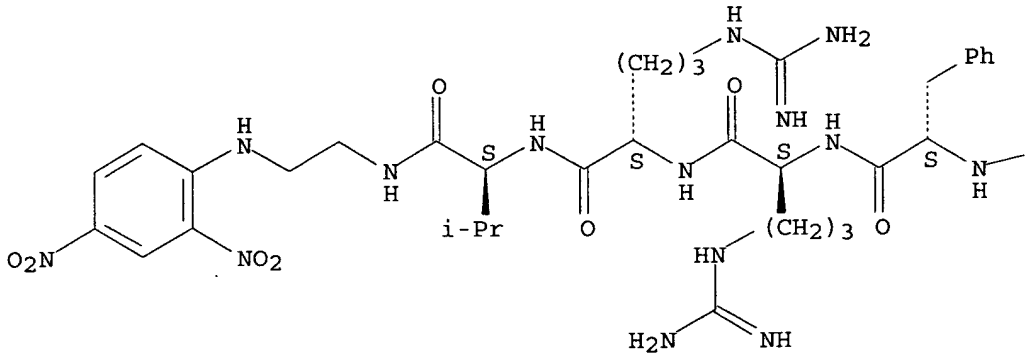
PAGE 1-B



RN 133839-16-4 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-arginyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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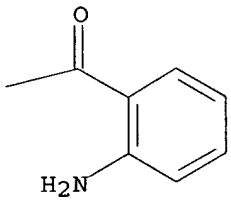
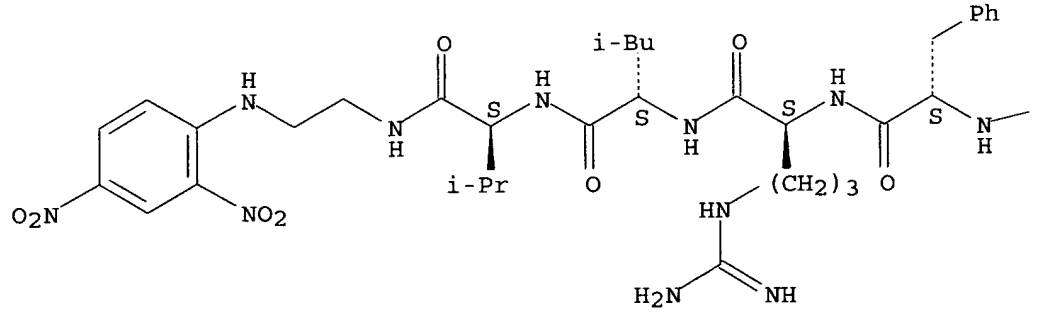


RN 162851-74-3 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-leucyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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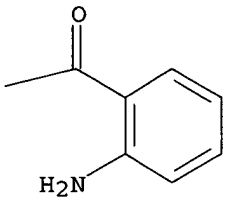
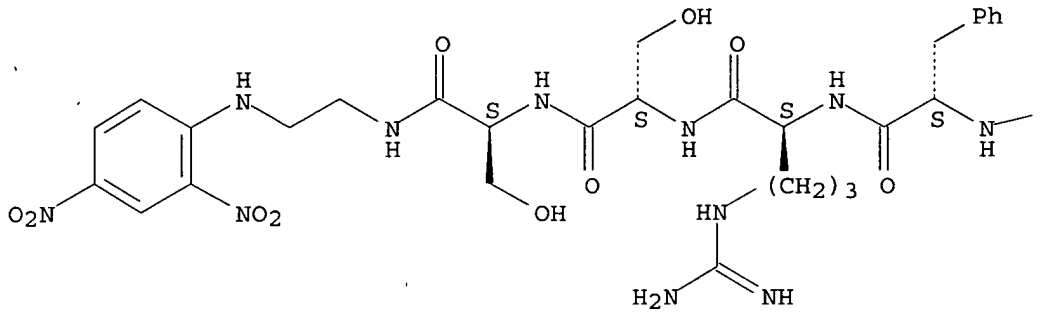


RN 162851-78-7 HCAPLUS
CN L-Serinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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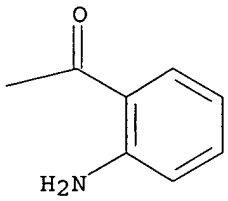


L11 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:66653 HCAPLUS
DOCUMENT NUMBER: 122:234165
TITLE: Fluorogenic peptide substrates for studies on the Arg-Ser and Met-Lys bond cleavage by tissue kallikrein (T-KK)
AUTHOR(S): Prado, Eline S.; Chagas, Jair R.; Juliano, Luiz
CORPORATE SOURCE: Dep. Biophysics, Escola Paulista de Medicina, Sao Paulo, 04044-020, Brazil
SOURCE: Pept. 1992, Proc. Eur. Pept. Symp., 22nd (**1993**), Meeting Date 1992, 931-2. Editor(s): Schneider, Conrad H.; Eberle, Alex N. ESCOM: Leiden, Neth.

CODEN: 60LUAN
DOCUMENT TYPE: Conference
LANGUAGE: English

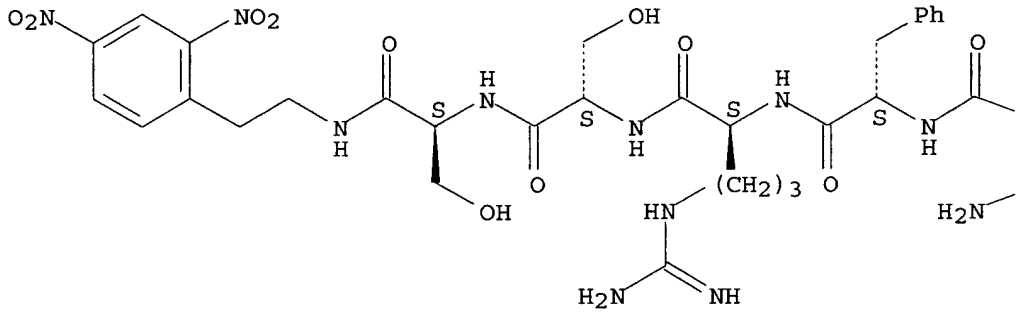
AB The kinetics of hydrolysis of 9 human kininogen-related fluorogenic peptides by human tissue kallikrein were determined and structure-activity relations were observed

IT **162128-88-3 162128-89-4**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(fluorogenic peptide substrates for studies of Arg-Ser and Met-Lys bond cleavage by human tissue kallikrein)

RN 162128-88-3 HCAPLUS
CN L-Serinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-(2,4-dinitrophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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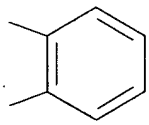
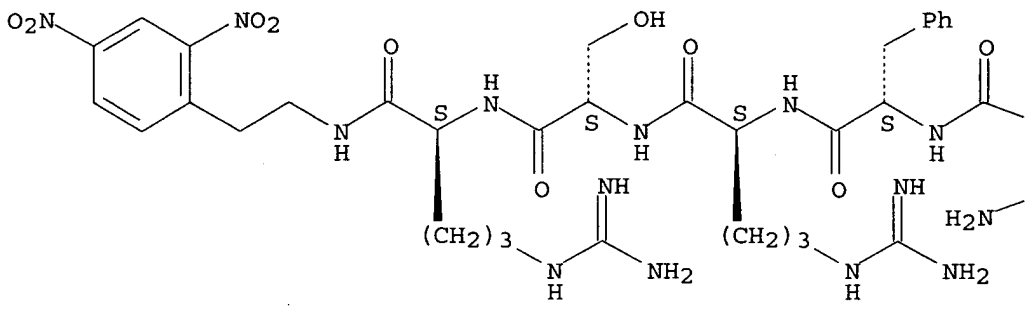


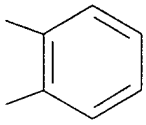
RN 162128-89-4 HCAPLUS
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-(2,4-dinitrophenyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L11 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:485790 HCAPLUS
DOCUMENT NUMBER: 117:85790
TITLE: Protein products of the rat kallikrein gene family. Substrate specificities of kallikrein rK2 (tonin) and kallikrein rK9
AUTHOR(S): Moreau, Thierry; Brillard-Bourdet, Michele; Bouhnik, Jacob; Gauthier, Francis
CORPORATE SOURCE: Fac. Med., Univ. Francois Rabelais, Tours, F-37032, Fr.
SOURCE: Journal of Biological Chemistry (**1992**), 267(14), 10045-51
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two closely related kallikrein-like proteinases having little activity toward the standard synthetic amide substrates of tissue kallikreins were isolated from the rat submandibular gland. They are the protein products of the rKlk2 (tonin) and the rKlk9 genes, as determined by amino acid sequence anal. (nomenclature of the genes and proteins of the kallikrein family is according to the proposal of the KININ '91 meeting held Sept. 8-14, 1991, in Munich, Germany). These 2 proteinases of similar structure also had very similar physicochem. properties. They differed from other kallikrein-related proteinases in having high pI values of 6.20 (rK2) and 6.85 (rK9). Kallikrein rK2 was purified as a single peptide chain, whereas rK9 appeared as a 2-chain protein after reduction Their enzymic properties were also very similar and differed significantly from those of other rat kallikrein-related proteinases. Unlike the 5 other kallikrein-related proteinases purified so far, kallikrein rK9 was not inhibited by aprotinin. RK9 also differed from rK2 by its tissue localization. The prostate gland contained only rK9, where it was the major kallikrein-like component. The amino acids preferentially

accommodated by the proteinase S3 to S2' subsites were identified using synthetic amide and protein substrates. Unlike other kallikrein-related proteinases, rK2 had a prevalent chymotrypsin-like specificity, whereas rK9 had both chymotrypsin-like and trypsinlike properties. Both rK2 and rK9 preferred a prolyl residue in position P2 of the substrate and did not accommodate bulky and hydrophobic residues at that position, as did most of the other kallikrein-related proteinases. This P2-proline-directed specificity is necessary for processing the precursors of several biol. active peptides. Subsites accommodating residues C-terminal to the scissile bond were also important in determining the substrate specificity of these proteinases. Both rK2 and rK9 showed a preference for hydrophobic residues in P2'. Other subsites upstream of the S3 subsite intervene in substrate binding and hydrolysis. The restricted specificity of rK2 and rK9 is consistent with the presence of an extended substrate binding site, and hence with a processing enzyme function. Their P1 specificities enabled both proteinases to release angiotensin II from angiotensinogen and from angiotensinogen I, but rK9 was at least 100 times less active than rK2 on both substrates. The substrate specificities of rK2 and rK9 were correlated with key amino acids defining their substrate binding site. The predicted preferential sequence(s) around the cleavage site deduced from these data may be used to identify the biol. substrate(s) of these proteinases.

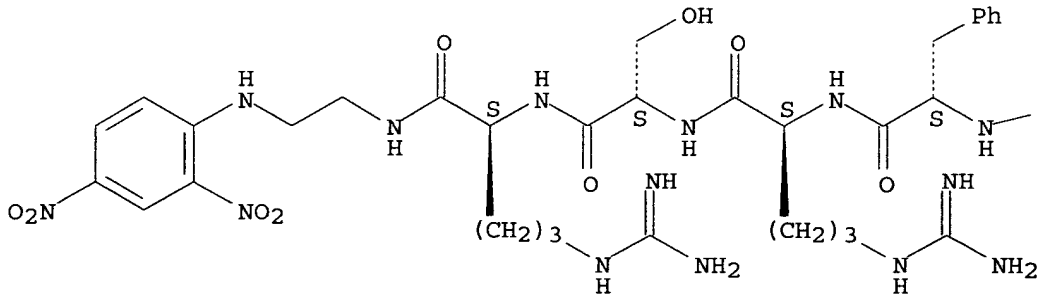
IT **133839-14-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with kallikrein-like proteinases rK2 and rK9, kinetics of)

RN 133839-14-2 HCAPLUS

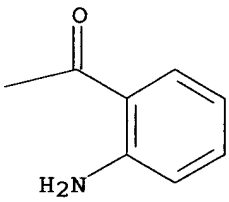
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L11 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:403159 HCAPLUS
DOCUMENT NUMBER: 117:3159
TITLE: Substrate specificities of tissue kallikrein and T-kininogenase: their possible role in kininogen processing
AUTHOR(S): Chagas, Jair R.; Hirata, Izaura Y.; Juliano, Maria A.; Xiong, William; Wang, Cindy; Chao, Julie; Juliano, Luiz; Prado, Eline S.
CORPORATE SOURCE: Dep. Biophys., Esc. Paul. Med., Sao Paulo, 04034, Brazil
SOURCE: Biochemistry (**1992**), 31(21), 4969-74
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

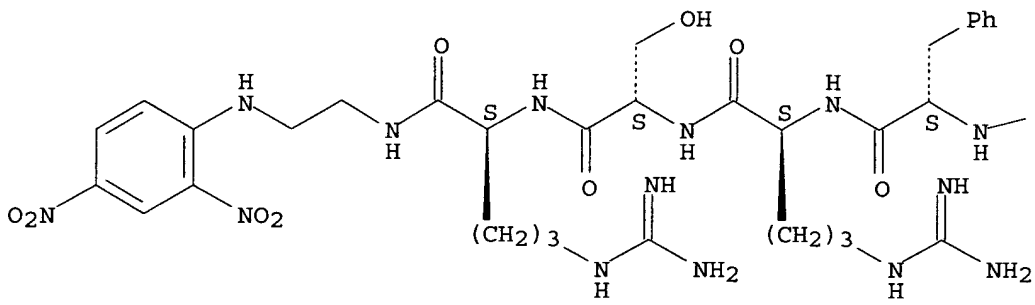
AB The present studies demonstrate the importance of subsite interactions in determining the cleavage specificities of kallikrein gene family proteinases. The effect of substrate amino acid residues in positions P3-P'3 on the catalytic efficiency of tissue kallikreins (rat, pig, and horse) and T-kininogenase was studied using peptidyl-pNA (pNA = p-nitroanilide) and intramol. quenched fluorogenic peptides as substrates. Kinetic analyses show the different effects of D-amino acid residues at P3, Pro at P'2, and Arg at either P'1 or P'3 on the hydrolysis of substrates by tissue kallikreins from rat and from horse or pig. T-kininogenase was shown to differ from tissue kallikrein in its interactions at subsites S2, S'1, and S'2. As a result of these differences, Abz-FRSR-EDDnp [(Abz = o-aminobenzoyl; EDDnp = N-(2,4-dinitrophenyl)ethylenediamine)] with Arg at P'2 is a good substrate for tissue kallikreins from horse, pig, and rat but not for T-kininogenase. Abz-FRRP-EDDnp and Abz-FRAPR-EDDnp with Pro at P'2 (rat high-mol.-weight kininogen sequence) are susceptible to rat tissue kallikrein but not to tissue kallikreins from horse and pig. Arg in P'3 increased the susceptibility of the Arg-Ala bond to rat tissue kallikrein. These data explain the release of bradykinin by rat tissue kallikrein and of kallidin by tissue kallikreins from other animal species. Abz-FRLV-EDDnp and Abz-FRLVR-EDDnp (T-kininogen sequence) are good substrates for T-kininogenase but not for tissue kallikrein. Arg at the leaving group (at either P'1, P'2, or P'3) lowers the Km values of T-kininogenase while Val and P'2 increases its kcat values. The results indicate that the enzyme subsites S'1, S'2, and S'3 are important determinants for the substrate specificity of tissue kallikreins and T-kininogenase. The findings are also in agreement with the known species specificity of tissue kallikreins and the resistance of rat T-kininogen to tissue kallikreins.

IT **133839-14-2 133839-15-3 133839-16-4**
RL: BIOL (Biological study)
(tissue kallikrein and T-kininogenase of mammal specificity for, reaction kinetics and structure relation to)

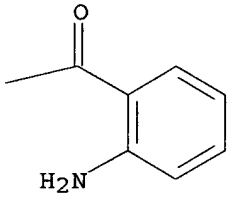
RN 133839-14-2 HCAPLUS
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



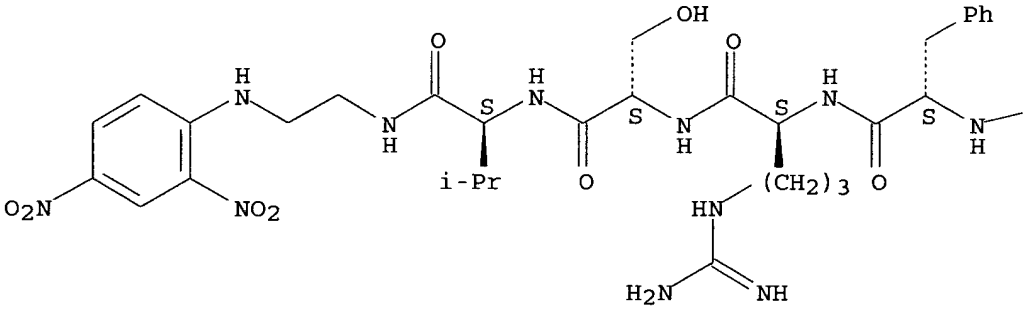
PAGE 1-B



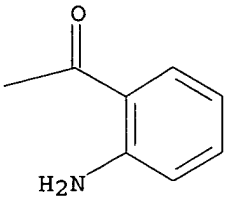
RN 133839-15-3 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



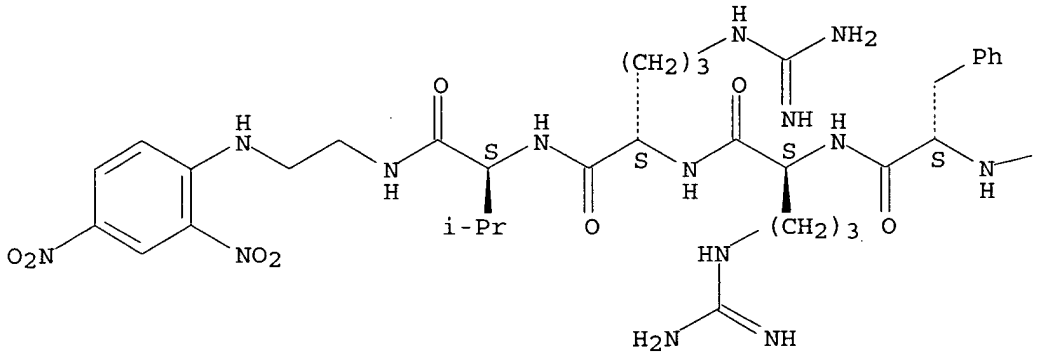
PAGE 1-B



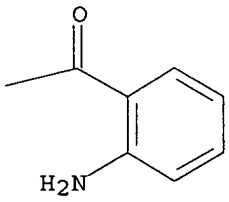
RN 133839-16-4 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-arginyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



L11 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:224299 HCAPLUS
DOCUMENT NUMBER: 114:224299
TITLE: Intramolecularly quenched fluorogenic tetrapeptide substrates for tissue and plasma kallikreins
AUTHOR(S): Chagas, Jair R.; Juliano, Luiz; Prado, Eline S.
CORPORATE SOURCE: Dep. Biophys., Es. Paulista Med., Sao Paulo, 04034, Brazil

SOURCE: Analytical Biochemistry (**1991**), 192(2), 419-25
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Five intramolecularly quenched fluorogenic substrates for arginyl hydrolases with the sequence Abz-Phe-Arg-X-Y--EDDnp (Abz = o-aminobenzoyl, EDDnp = ethylenediamine dinitrophenyl X = Arg or Ser; Y = Val, Pro, or Arg) were synthesized by classical solution methods. Kinetics of their hydrolysis by tissue and plasma kallikreins, trypsin, and thrombin characterized Abz-Phe-Arg-Ser-Arg-EDDnp as a specific and sensitive substrate for the continuous assay of tissue kallikreins while Abz-Phe-Arg-Arg-Pro-EDDnp was the best substrate for human plasma kallikrein. The 5 peptides were poor substrates for trypsin and resistant to thrombin.

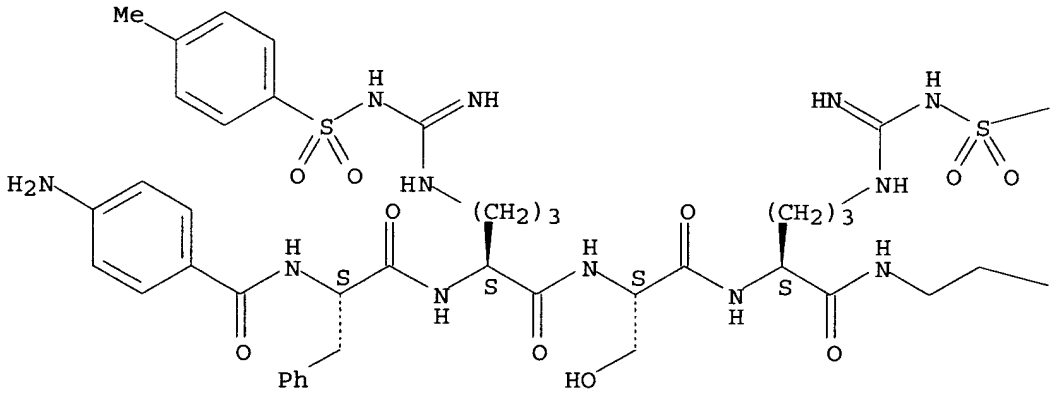
IT **133855-69-3P 133855-70-6P 133855-72-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and detosylation of)

RN 133855-69-3 HCAPLUS

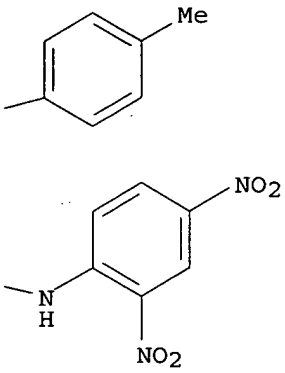
CN L-Ornithinamide, N-(4-aminobenzoyl)-L-phenylalanyl-N5-[imino[[(4-methylphenyl)sulfonyl]amino]methyl]-L-ornithyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]-N5-[imino[[(4-methylphenyl)sulfonyl]amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



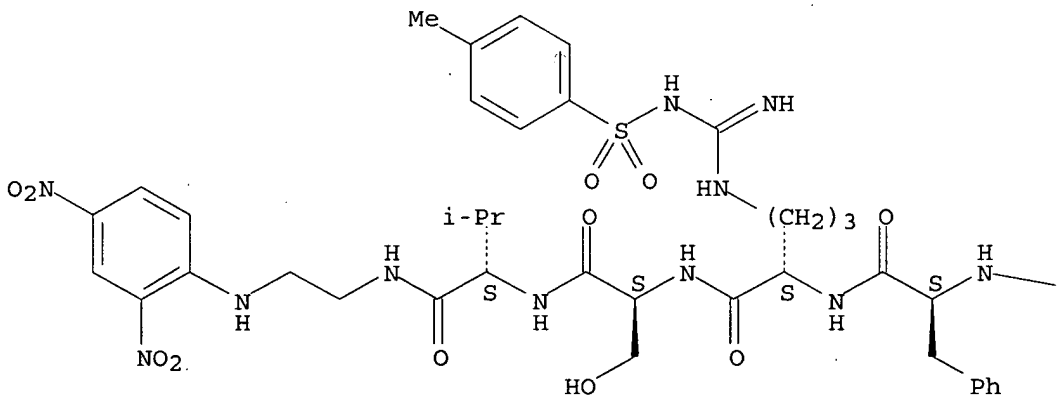
PAGE 1-B



RN 133855-70-6 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-N5-[imino[[(4-methylphenyl)sulfonyl]amino]methyl]-L-ornithyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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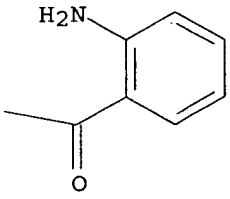
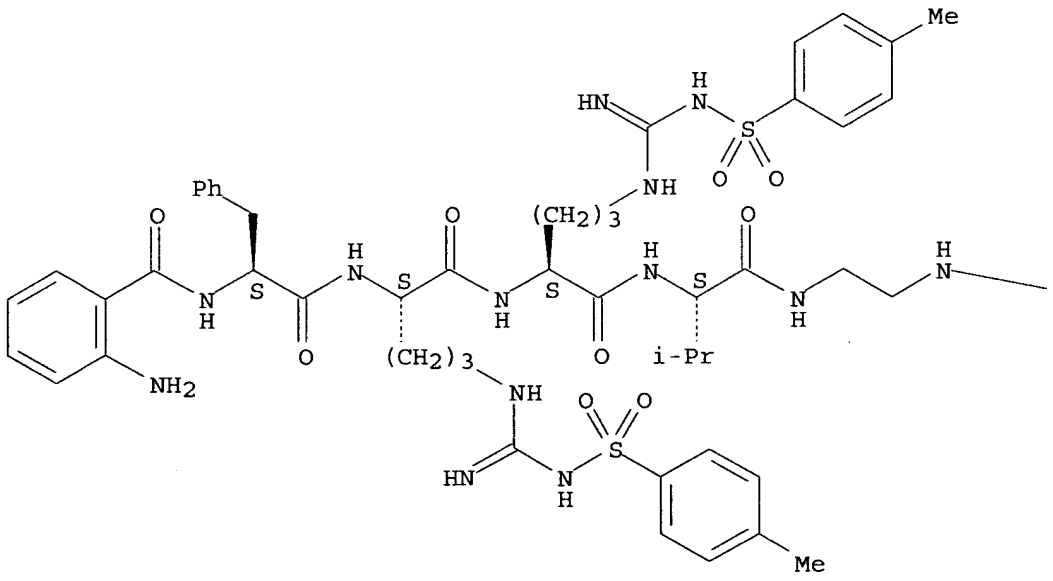


RN 133855-72-8 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-N5-[imino[[(4-methylphenyl)sulfonyl]amino]methyl]-L-ornithyl-N5-[imino[[(4-methylphenyl)sulfonyl]amino]methyl]-L-ornithyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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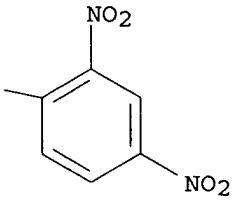
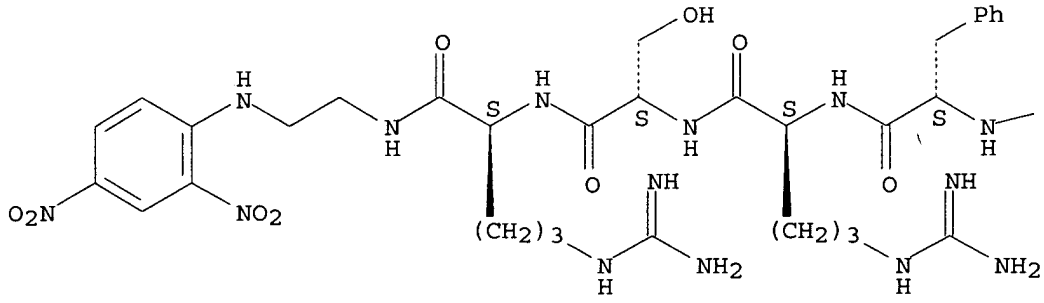


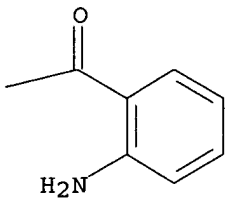
IT **133839-14-2P 133839-15-3P 133839-16-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intramolecularly quenched fluorogenic substrates for tissue and plasma kallikreins)
RN 133839-14-2 HCAPLUS
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



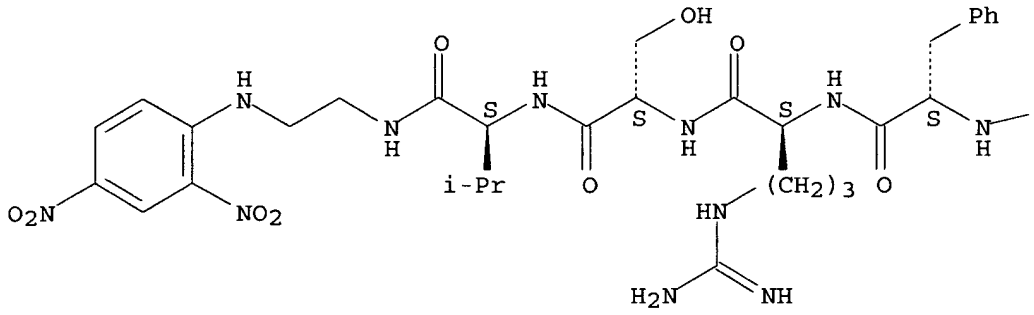
PAGE 1-B



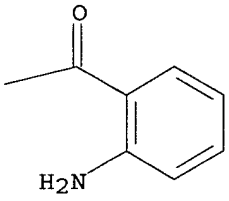
RN 133839-15-3 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



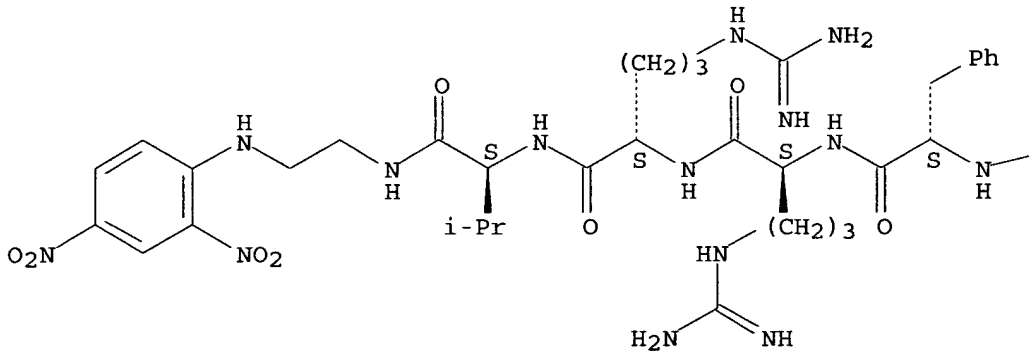
PAGE 1-B

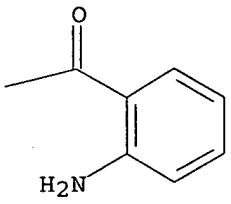


RN 133839-16-4 HCAPLUS
CN L-Valinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-arginyl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



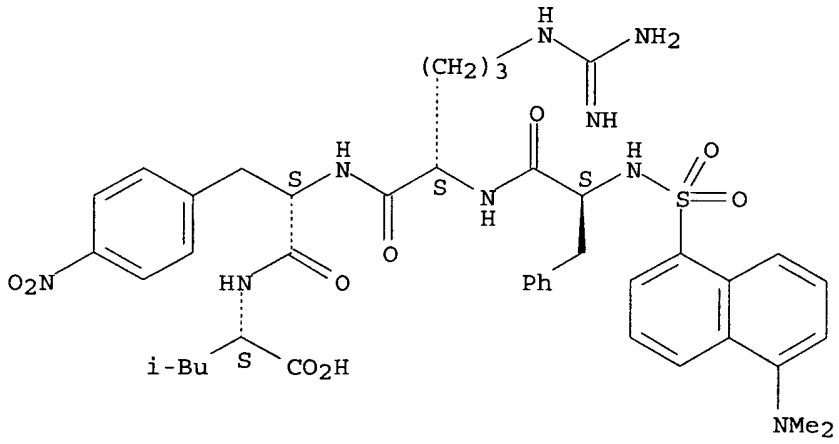


L11 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:614089 HCAPLUS
DOCUMENT NUMBER: 107:214089
TITLE: Chromophoric and fluorophoric peptide substrates cleaved through the dipeptidyl carboxypeptidase activity of cathepsin B
AUTHOR(S): Pohl, Jan; Davinic, Silvia; Blaha, Ivo; Strop, Petr; Kostka, Vladimir
CORPORATE SOURCE: Inst. Org. Chem. Biochem., Czech. Acad. Sci., Prague, CS-16610, Czech.
SOURCE: Analytical Biochemistry (**1987**), 165(1), 96-101
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The action of bovine spleen cathesin B as a dipeptidyl carboxypeptidase on newly synthesized substrates of the type peptidyl-X-p-nitrophenylalanyl (Phe(NO2))-Y (where X,Y = amino acid residue) or 5-dimethylaminonaphthalene-1-sulfonyl (Dns)-peptidyl-X-Phe(NO2)-Y was investigated. The kinetic parameters of hydrolysis of the X-Phe(NO2) bond were determined by difference spectrophotometry ($\Delta\varepsilon$310 = 1600 M-1 cm-1) or by spectrofluorometry by following the 5-8-fold increase of Dns-group fluorescence (excitation at 350 nm and emission at 535 nm). The substrates were moderately sensitive to cathepsin B; kcat (the catalytic constant) was 0.7-s-1 at pH 5 and 25° and Km was 6-240 μM. The very acidic optima of pH 4-5 are characteristic for the dipeptidyl carboxypeptidase activity of cathepsin B. Bovine spleen cathepsins S and H had little and no activity, resp., when assayed with Pro-Glu-Ala-Phe(NO2)-Gly. These peptides should be a valuable tool for routine assays and for mechanistic studies on cathepsin B.

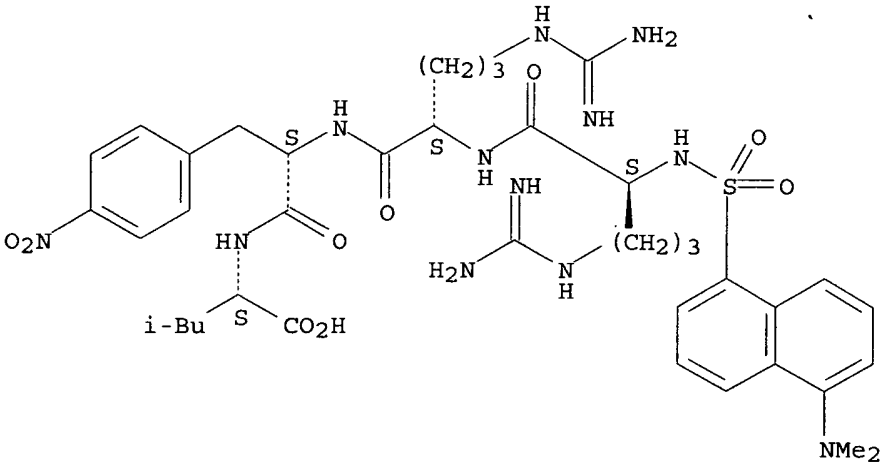
IT **108204-50-8 108204-51-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with cathepsin B, kinetics and mechanism of)
RN 108204-50-8 HCAPLUS
CN L-Leucine, N-[N-[N2-[N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-phenylalanyl]-L-arginyl]-4-nitro-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 108204-51-9 HCAPLUS
CN L-Leucine, N-[N-[N2-[N2-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-arginyl]-L-arginyl]-4-nitro-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L11 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:191672 HCAPLUS
DOCUMENT NUMBER: 106:191672
TITLE: A study of the peptidyldipeptidase activity of bovine spleen cathepsin B using synthetic substrates
AUTHOR(S): Pohl, J.; Davinic, S.; Blaha, I.; Strop, P.; Kostka, V.
CORPORATE SOURCE: Inst. Org. Chem. Biochem., Czech. Acad. Sci., Prague, CS-166 10, Czech.
SOURCE: Cysteine Proteinases Their Inhib., Proc. Int. Symp., 1st (1986), Meeting Date 1985, 73-8.
Editor(s): Turk, Vito. de Gruyter: Berlin, Fed. Rep. Ger.
CODEN: 55LGA3
DOCUMENT TYPE: Conference

LANGUAGE: English

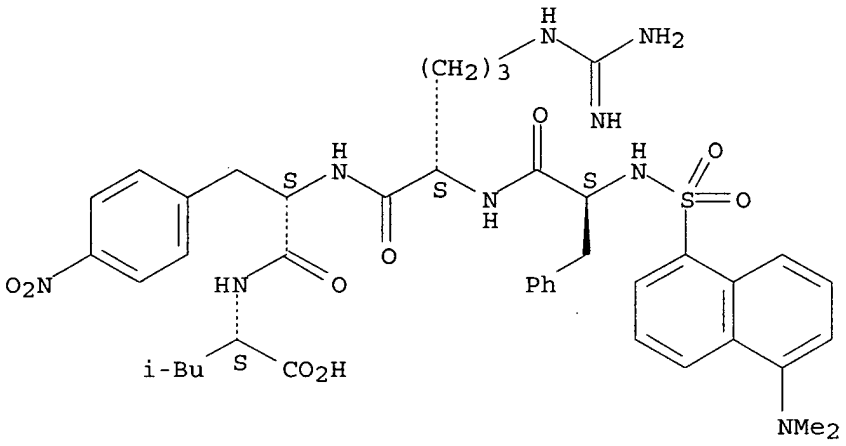
AB Fundamental kinetic data characterizing the peptidyldipeptidase action of cathepsin B on chromophoric and fluorophoric synthetic substrates are reported.

IT **108204-50-8 108204-51-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with peptidyldipeptidase of cathepsin B of spleen, kinetics of)

RN 108204-50-8 HCAPLUS

CN L-Leucine, N-[N-[N2-[N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-phenylalanyl]-L-arginyl]-4-nitro-L-phenylalanyl]- (9CI) (CA INDEX NAME)

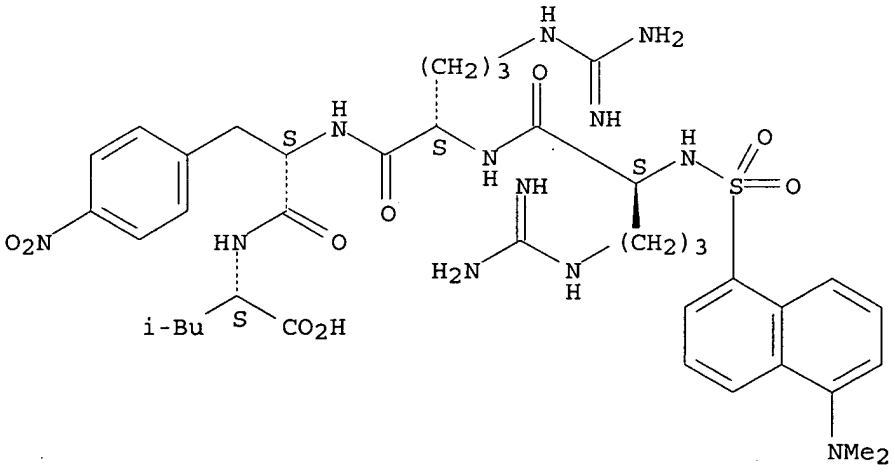
Absolute stereochemistry.



RN 108204-51-9 HCAPLUS

CN L-Leucine, N-[N-[N2-[N2-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-arginyl]-L-arginyl]-4-nitro-L-phenylalanyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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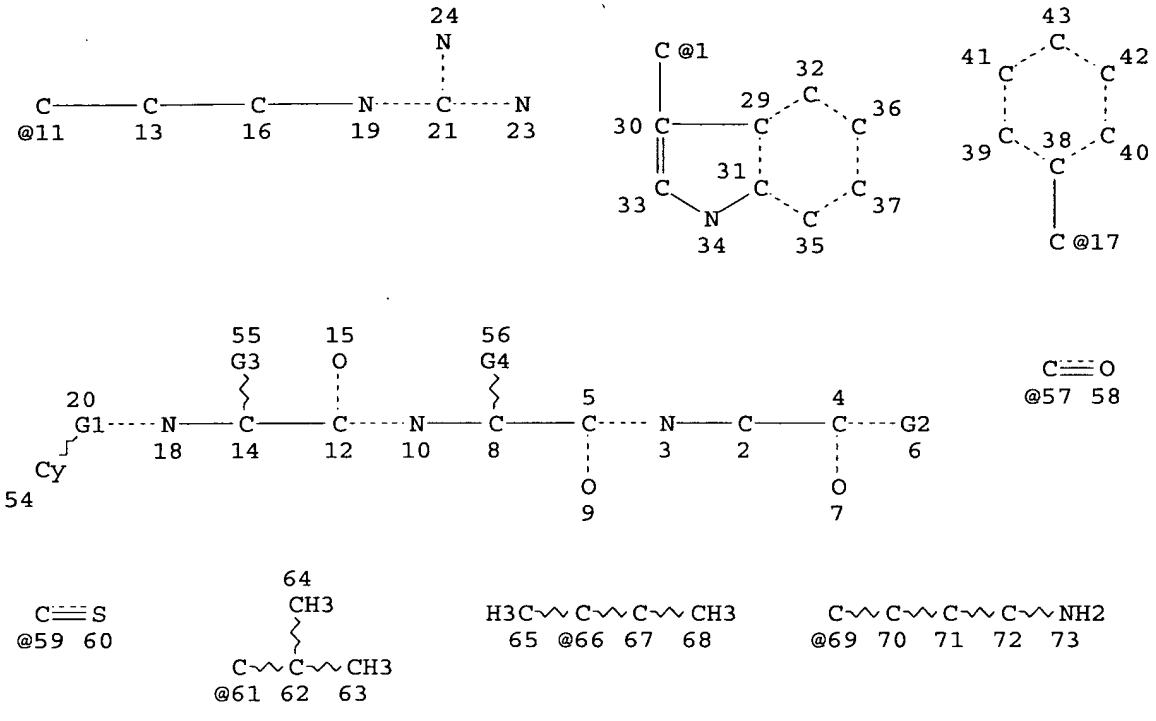

84

Page 1-A

Page 2-A
VAR G1=57/59/S
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VAR G3=61/66/11/69/17/1
VAR G4=11/69
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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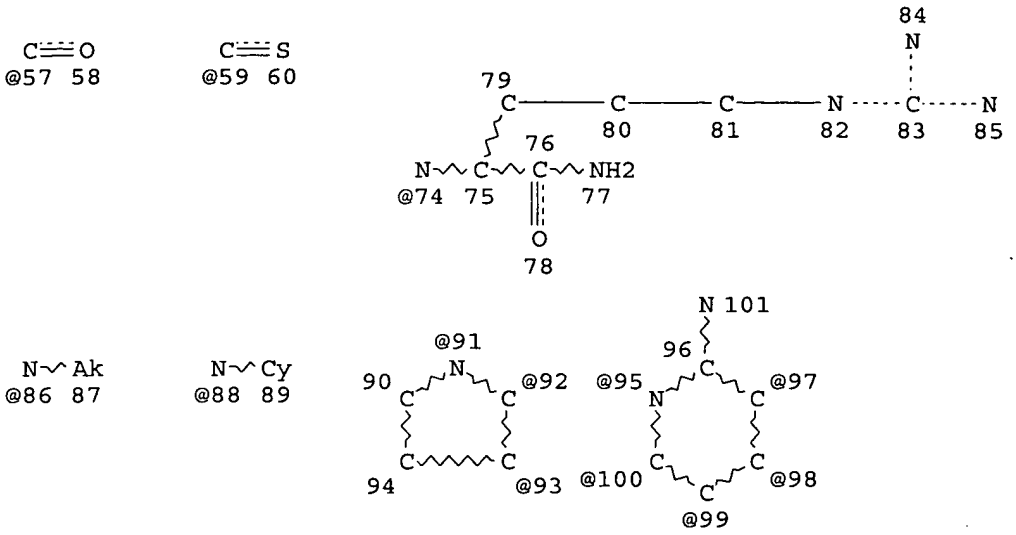
STEREO ATTRIBUTES: NONE
L6 12249 SEA FILE=REGISTRY SSS FUL L4
L7 STR



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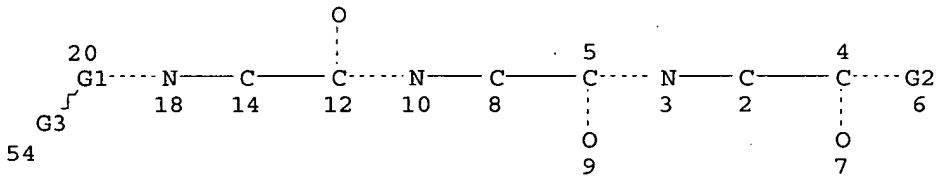
Page 1-A



Page 2-A
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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 47

STEREO ATTRIBUTES: NONE
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L9 85 SEA FILE=REGISTRY ABB=ON PLU=ON L8 AND SQL=<4
L10 40 SEA FILE=HCAPLUS ABB=ON PLU=ON L9
L11 13 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND PD=<DECEMBER 15, 1998

L12 27 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 NOT L11

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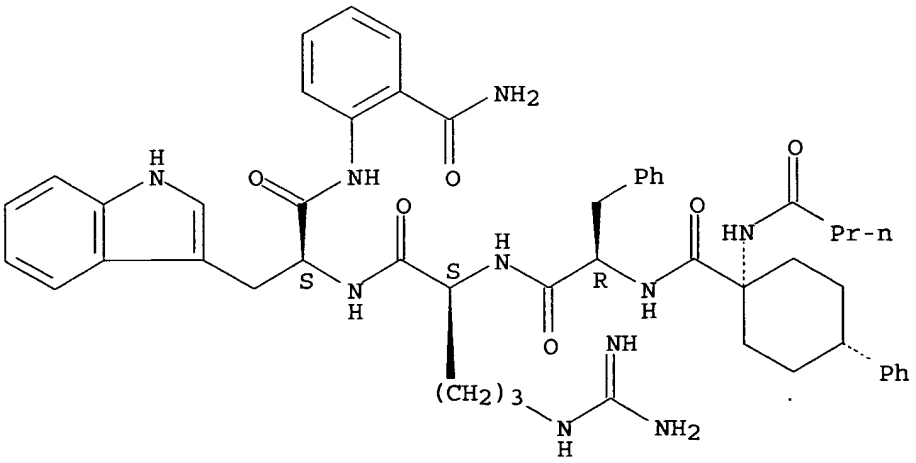
L12 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1178234 HCAPLUS
DOCUMENT NUMBER: 144:88541
TITLE: Preparation of human Melanocortin-4 receptor agonist libraries: linear peptides X-Y-DPhe7-Arg8-Trp(or 2-Nal)9-Z-NH2
AUTHOR(S): Cheung, Adrian Wai-Hing; Qi, Lida; Gore, Vijay; Chu, Xin-Jie; Bartkovitz, David; Kurylko, Grazyna; Swistok, Joseph; Danho, Waleed; Chen, Li; Yagaloff, Keith
CORPORATE SOURCE: Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ, 07110, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(24), 5504-5508
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two libraries of hMC4R agonists, X-Y-DPhe7-Arg8-2-Nal9-Z-NH2 and X-Y-DPhe7-Arg8-Trp9-Z-NH2, totaling 185 peptides were prepared using Irori radiofrequency tagging technol. and Argonaut Quest 210 Synthesizer, where X stands for N-caps, Y for His6 surrogates and Z for Gly10 surrogates. As a result of this study, His-modified pentapeptides with Trp were found to be more hMC4R potent than the corresponding 2-Nal analogs, novel N-caps and Gly surrogates were identified and 19 new peptides which are potent hMC4R agonists (EC50 1-15 nM) and selective against hMC1R were discovered.

IT **365552-10-9P 365552-13-2P 365552-15-4P**
365552-16-5P 365552-17-6P 365552-20-1P
365552-23-4P 365552-25-6P 365552-35-8P
365552-38-1P 365552-40-5P 365552-97-2P
365552-99-4P 365553-01-1P 365553-09-9P
RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation)
(preparation of peptides X-Y-DPhe7-Arg8-Trp(or 2-Nal)9-Z-NH2 as human melanocortin-4 receptor agonists)

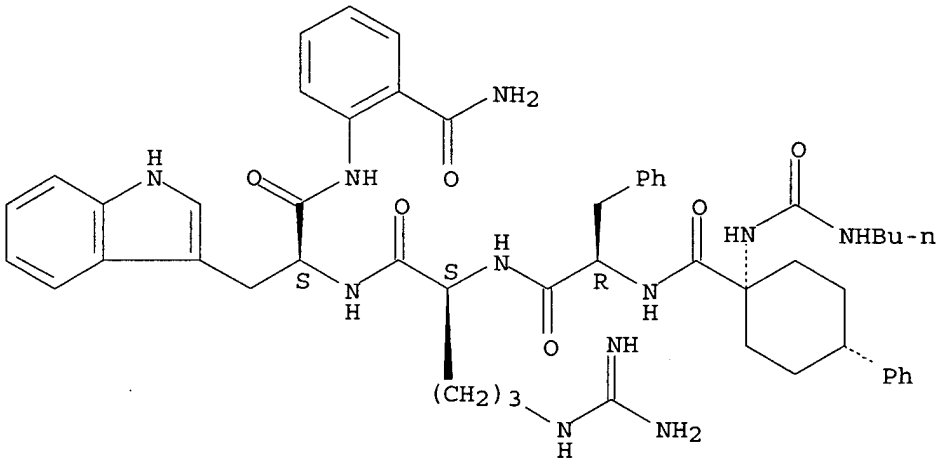
RN 365552-10-9 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



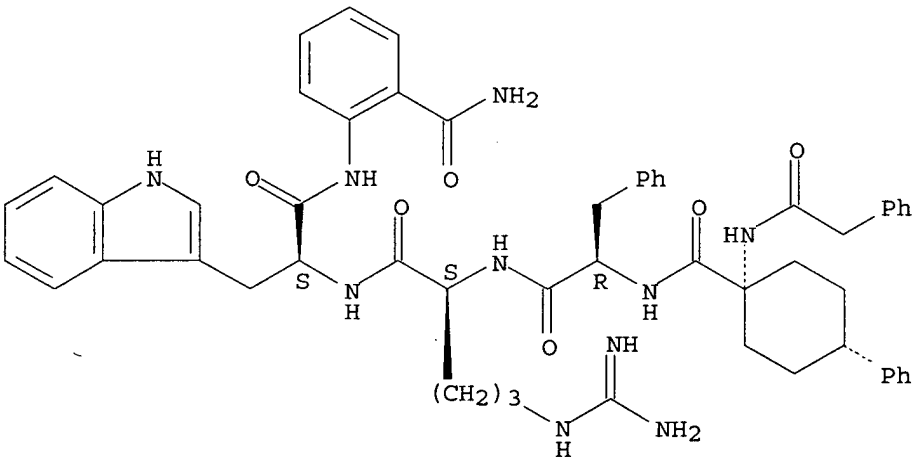
RN 365552-13-2 HCAPLUS
CN L-Tryptophanamide, cis-1-[[(butylamino)carbonyl]amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



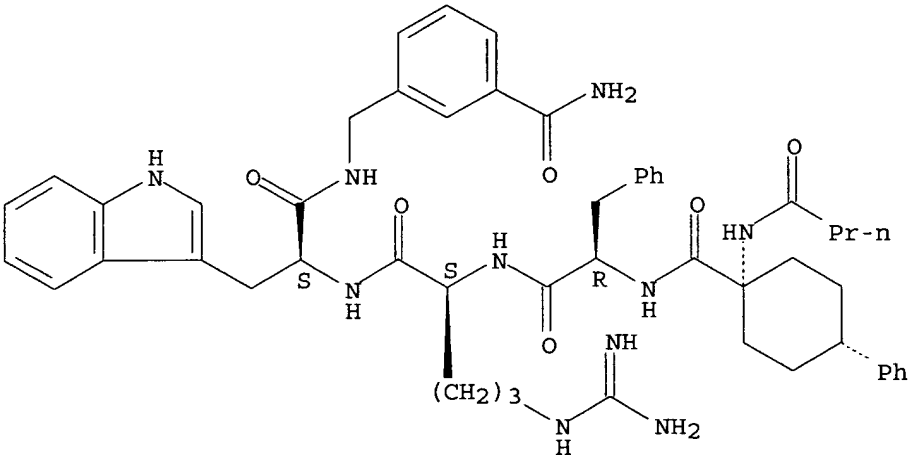
RN 365552-15-4 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



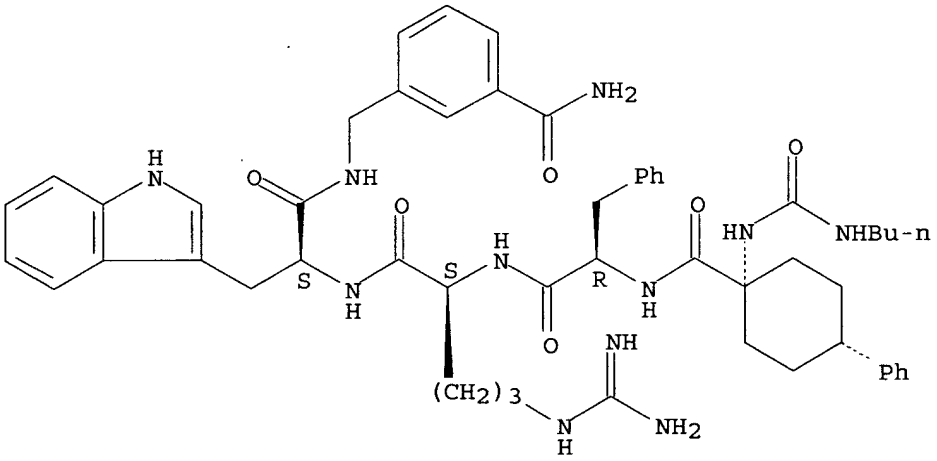
RN 365552-16-5 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



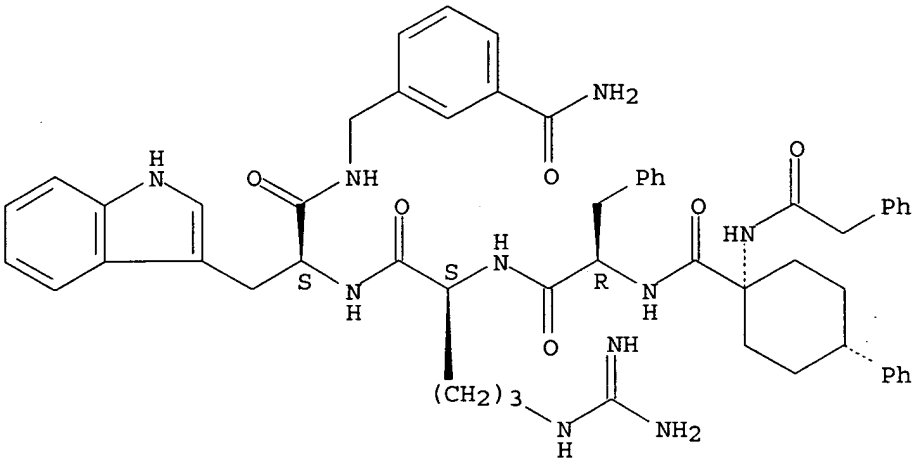
RN 365552-17-6 HCAPLUS
CN L-Tryptophanamide, cis-1-[[(butylamino)carbonyl]amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



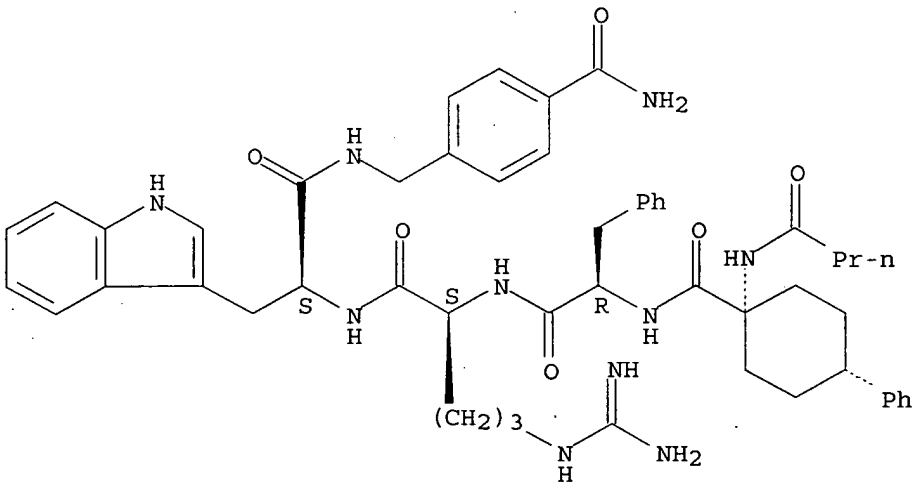
RN 365552-20-1 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



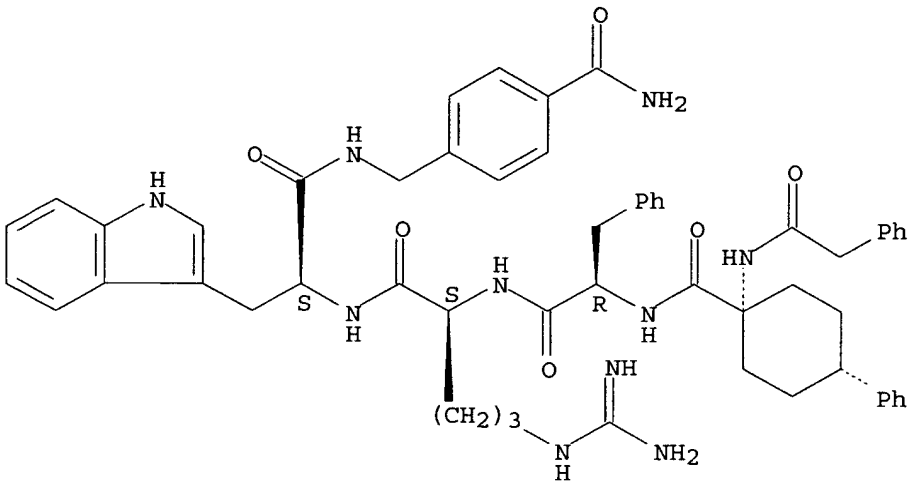
RN 365552-23-4 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



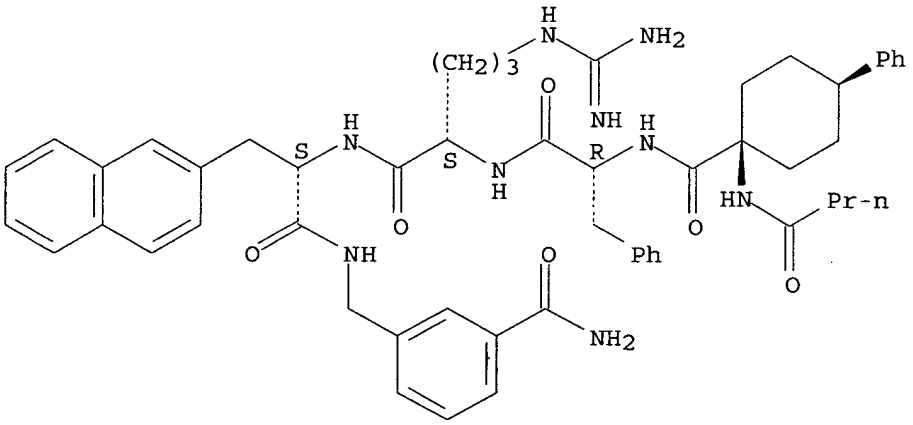
RN 365552-25-6 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



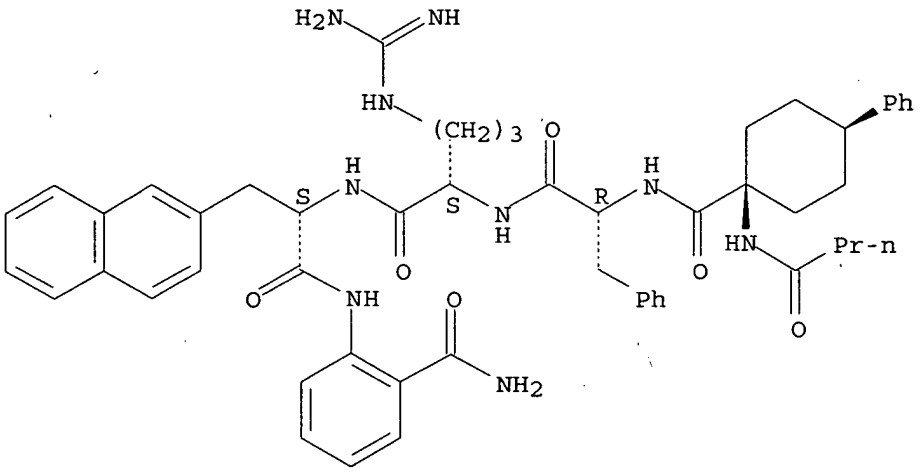
RN 365552-35-8 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



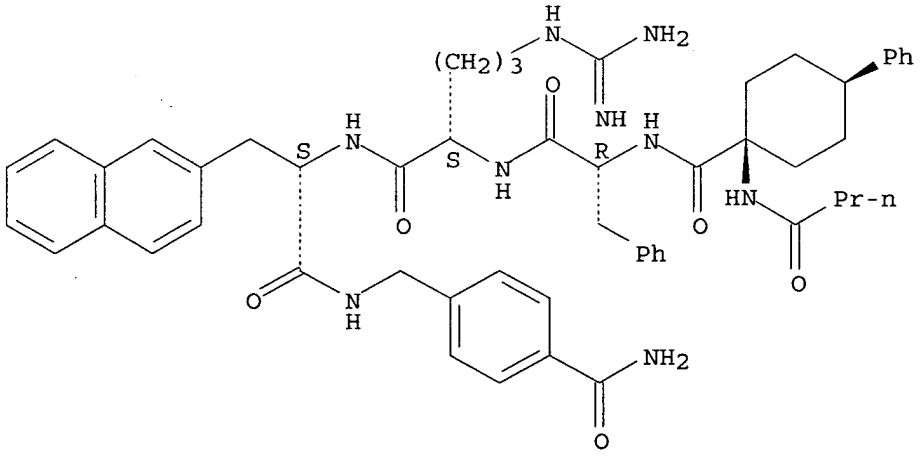
RN 365552-38-1 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



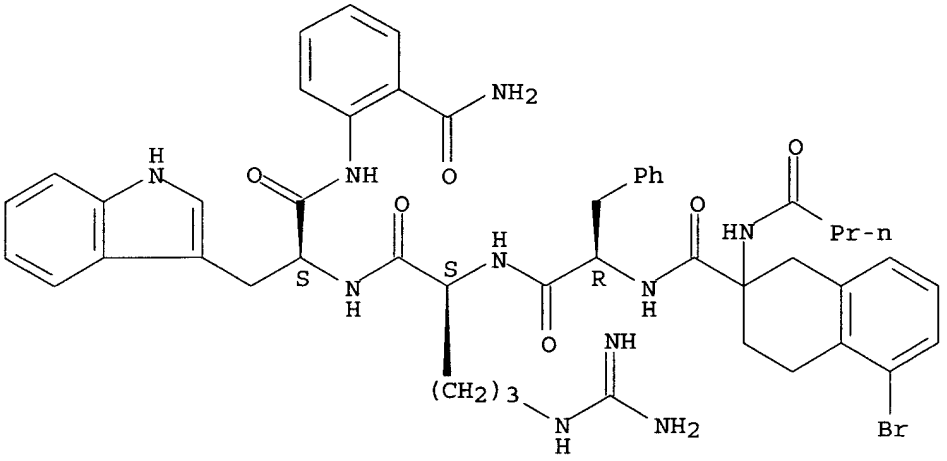
RN 365552-40-5 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



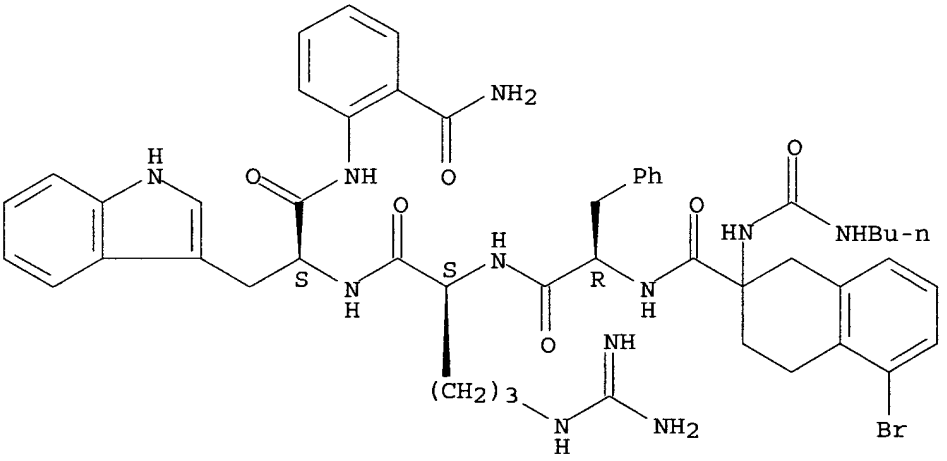
RN 365552-97-2 HCAPLUS
CN L-Tryptophanamide, 5-bromo-1,2,3,4-tetrahydro-2-[(1-oxobutyl)amino]-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 365552-99-4 HCAPLUS
CN L-Tryptophanamide, 5-bromo-2-[[(butylamino)carbonyl]amino]-1,2,3,4-tetrahydro-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 365553-01-1 HCAPLUS
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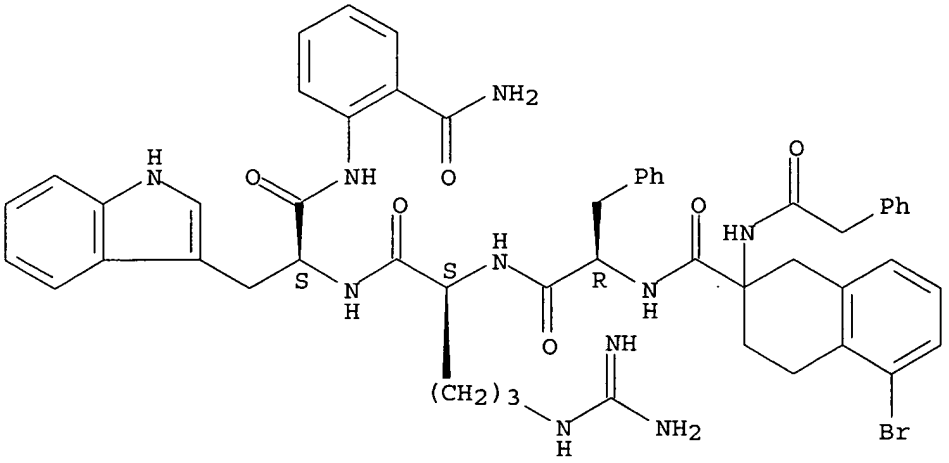
Absolute stereochemistry.



RN 365553-09-9 HCAPLUS
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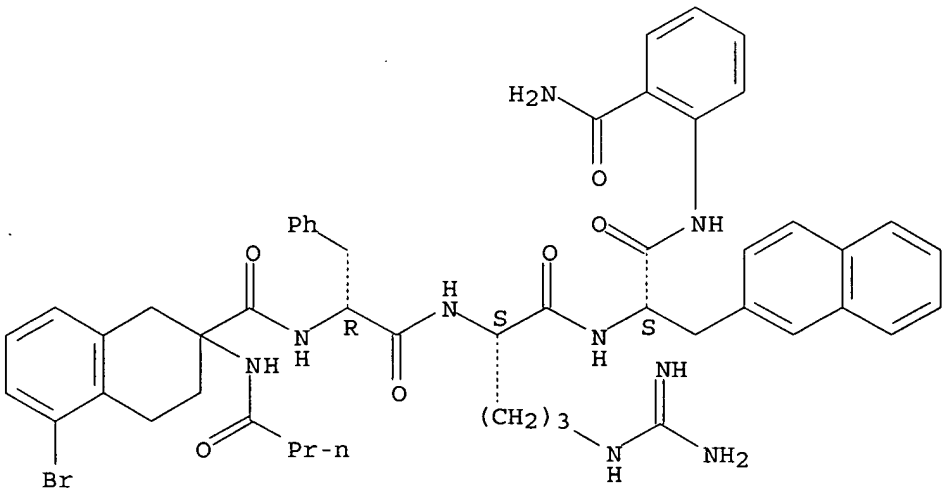
Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1119781 HCAPLUS
DOCUMENT NUMBER: 144:22999
TITLE: Antibacterial activities of ferrocenoyl- and cobaltocenium-peptide bioconjugates
AUTHOR(S): Chantson, Janine T.; Falzacappa, Maria Vittoria Verga; Crovella, Sergio; Metzler-Nolte, Nils
CORPORATE SOURCE: Department of Chemistry, University of Pretoria, Pretoria, 0002, S. Afr.
SOURCE: Journal of Organometallic Chemistry (2005), 690(21-22), 4564-4572

CODEN: JORCAI; ISSN: 0022-328X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The peptide and metallocene-peptide bioconjugates R-Arg-Arg-Phe-NH2, R-Phe-Arg-Phe-NH2 where R = H, Fe(Cp)(C5H4-CO), Co(Cp)(C5H4-CO)+ and R'-Gly-Trp-Arg-Arg-Phe-NH2, R'-Trp-Arg-Arg-Phe-NH2, where R' = n-C5H11CO, Fe(Cp)(C5H4-CO), Co(Cp)(C5H4-CO)+, and Arg = L-arginine, Gly = L-glycine, Phe = L-phenylalanine, Trp = L-tryptophan were prepared by solid phase peptide synthesis (SPPS). The compds. were purified by RP-HPLC and characterized by ESI-MS and NMR spectroscopy. Antibacterial properties of the compds. were determined by min. inhibitory concentration (MIC) tests against
Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.

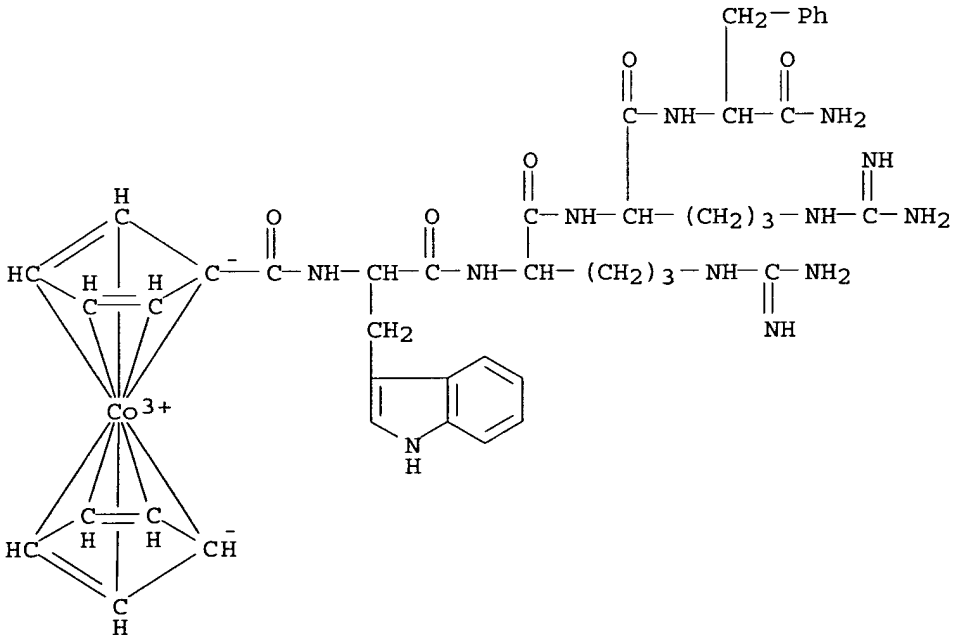
IT **870487-01-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid phase synthesis and antibacterial activities of ferrocenoyl- and cobaltocenium-peptide bioconjugates)

RN 870487-01-7 HCAPLUS

CN L-Phenylalaninamide, N-(cobaltoceniumylcarbonyl)-L-tryptophyl-L-arginyl-L-arginyl-, salt with trifluoroacetic acid (1:1) (9CI) (CA INDEX NAME)

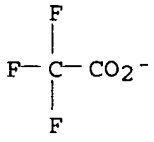
CM 1

CRN 870487-00-6
CMF C43 H54 Co N12 O5
CCI CCS



CM 2

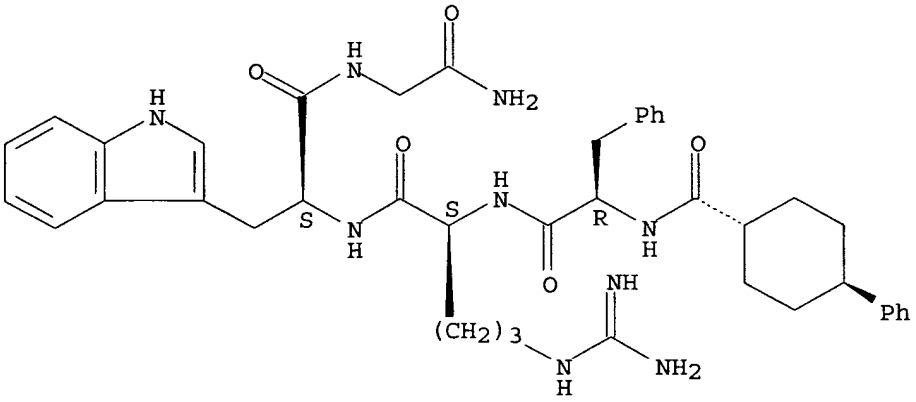
CRN 14477-72-6
CMF C2 F3 O2



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1084905 HCAPLUS
DOCUMENT NUMBER: 143:415599
TITLE: Discovery of 1-amino-4-phenylcyclohexane-1-carboxylic acid and its influence on agonist selectivity between human melanocortin-4 and -1 receptors in linear pentapeptides
AUTHOR(S): Chu, Xin-Jie; Bartkovitz, David; Danho, Waleed; Swistok, Joseph; Cheung, Adrian Wai-Hing; Kurylko, Grazyna; Rowan, Karen; Yeon, Mitch; Franco, Lucia; Qi, Lida; Chen, Li; Yagaloff, Keith
CORPORATE SOURCE: Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ, 07110, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2005), 15(22), 4910-4914
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Linear pentapeptides (Penta-cis-Apc-DPhe-Arg-Trp-Gly-NH2) containing 1-amino-4-phenylcyclohexane-1-carboxylic acid (cis-Apc) and substituted Apc are potent hMC4R agonists and they are inactive or weakly active in hMC1R, hMC3R, and hMC5R agonist assays. This study, together with our earlier report on 5-BrAtc, demonstrated the importance of replacing His6 with phenyl-containing rigid templates in achieving good hMC4R agonist potency and selectivity against hMC1R in linear pentapeptides.
IT **868141-25-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(discovery of 1-amino-4-phenylcyclohexane-1-carboxylic acid and its influence on agonist selectivity between human melanocortin-4 and -1 receptors in linear pentapeptides)
RN 868141-25-7 HCAPLUS
CN Glycinamide, N-[(trans-4-phenylcyclohexyl)carbonyl]-D-phenylalanyl-L-arginyl-L-tryptophyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1028254 HCAPLUS
DOCUMENT NUMBER: 143:472808
TITLE: Structure-activity relationship of linear tetrapeptides Tic-DPhe-Arg-Trp-NH2 at the human melanocortin-4 receptor and effects on feeding behaviors in rat
AUTHOR(S): Ye, Zhixiong; MacNeil, Tanya; Weinberg, David H.; Kalyani, Rubana N.; Tang, Rui; Strack, Alison M.; Murphy, Beth A.; Mosley, Ralph T.; MacIntyre, D. Euan; Van der Ploeg, Lex H. T.; Patchett, Arthur A.; Wyvratt, Matthew J.; Nargund, Ravi P.
CORPORATE SOURCE: Department of Medicinal Chemistry, Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Peptides (New York, NY, United States) (2005), 26(10), 2017-2025
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The melanocortin subtype-4 receptor (MC4R) has been implicated in the control of feeding behavior and body weight regulation. A series of tetrapeptides, based on Tic-DPhe-Arg-Trp-NH2-a mimic of the putative message sequence "His-Phe-Arg-Trp" and modified at the DPhe position, were prepared and pharmacol. characterized for potency and selectivity. Substitution of His with Tic gave peptides with significant increases in selectivity. The effects of the substitution pattern of DPhe were investigated and it has significant influences on potency and the level of the maximum cAMP accumulation. Intracerebroventricular administration of peptide 10 induced significant inhibition of cumulative overnight food intake and feeding duration in rats.

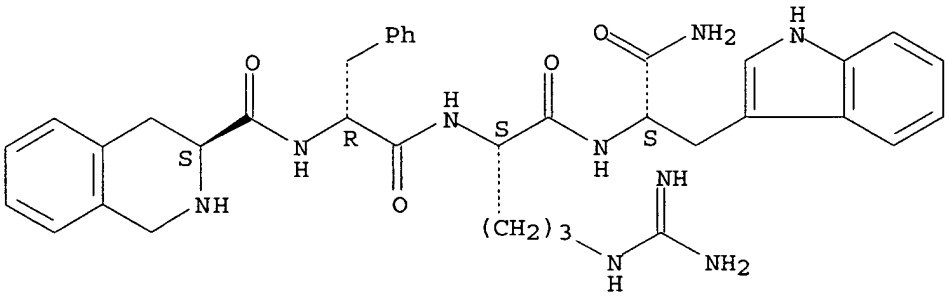
IT **869789-47-9 869789-48-0 869789-49-1**
869789-50-4 869789-51-5 869789-52-6
869789-53-7 869789-54-8 869789-55-9
869789-56-0 869789-57-1 869789-58-2
869789-59-3 869789-60-6 869789-61-7
869789-62-8 869789-63-9 869789-64-0
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(structure-activity relationship of linear tetrapeptides at human

melanocortin-4 receptor and effects on feeding behaviors in rat)

RN 869789-47-9 HCAPLUS

CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

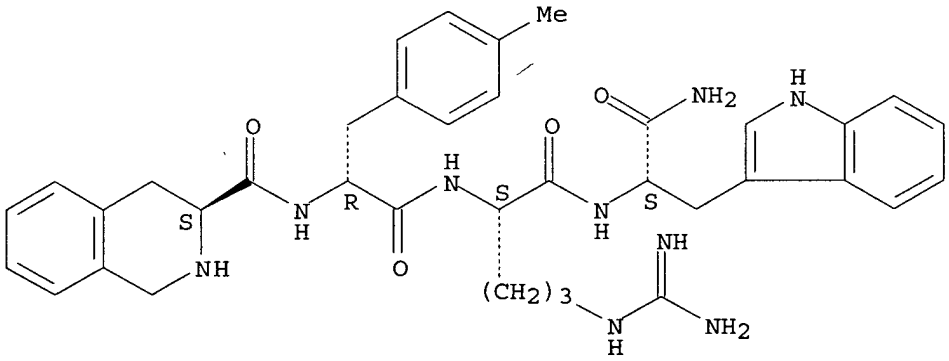
Absolute stereochemistry.



RN 869789-48-0 HCAPLUS

CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-methyl-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

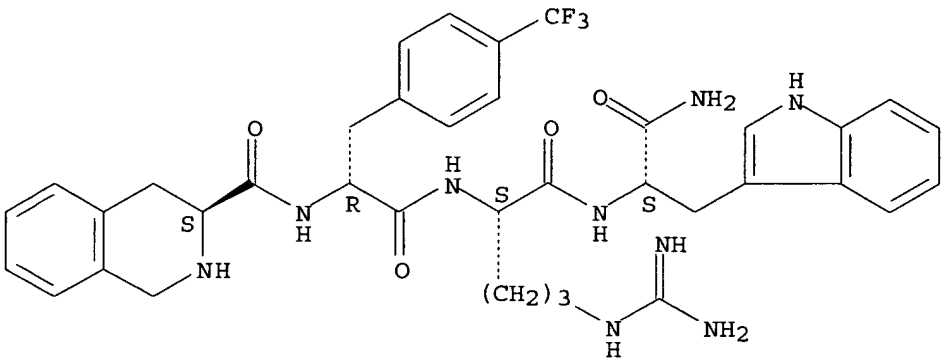
Absolute stereochemistry.



RN 869789-49-1 HCAPLUS

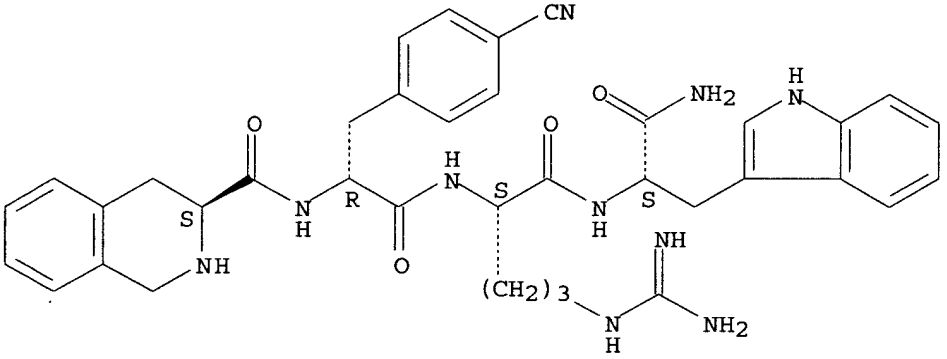
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-(trifluoromethyl)-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



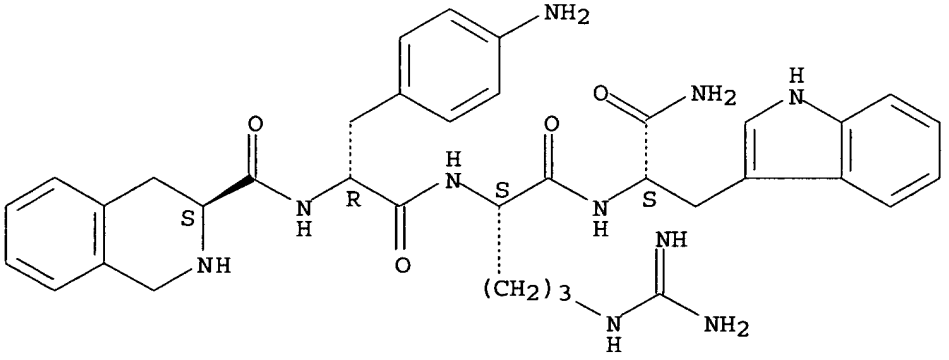
RN 869789-50-4 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-cyano-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 869789-51-5 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-amino-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

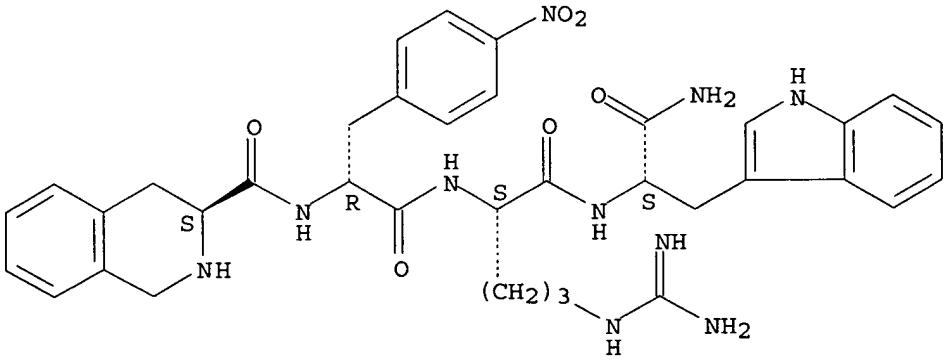
Absolute stereochemistry.



RN 869789-52-6 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-nitro-

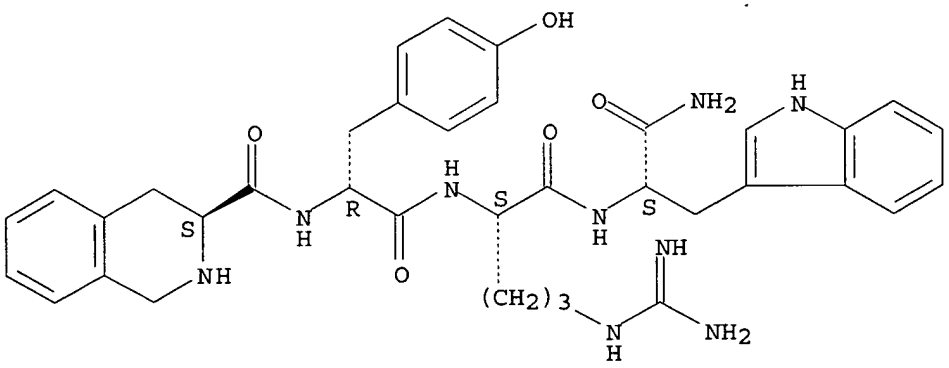
D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



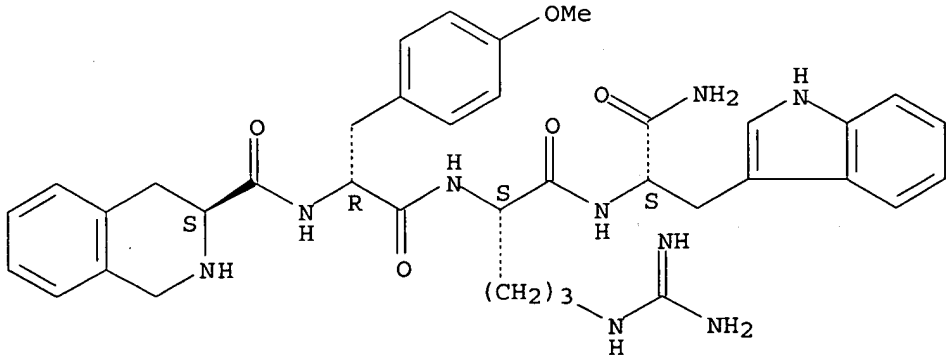
RN 869789-53-7 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-D-tyrosyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



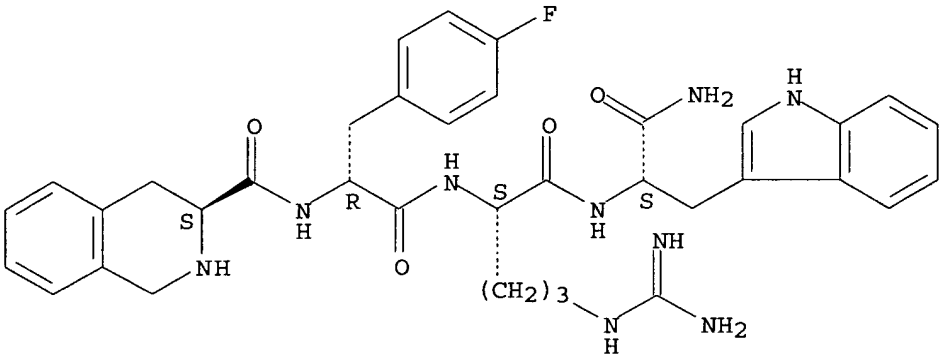
RN 869789-54-8 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-O-methyl-D-tyrosyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



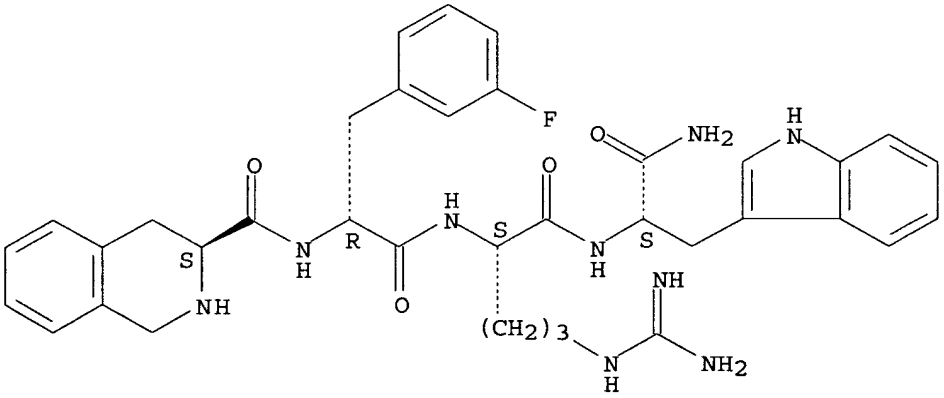
RN 869789-55-9 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-fluoro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



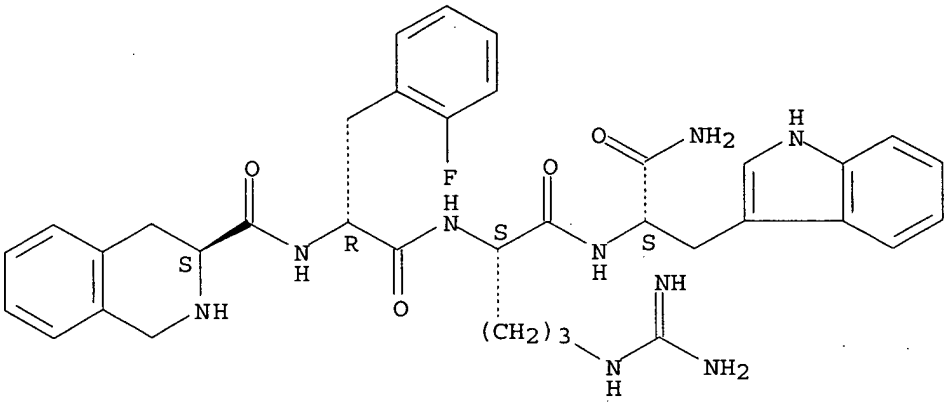
RN 869789-56-0 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-3-fluoro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



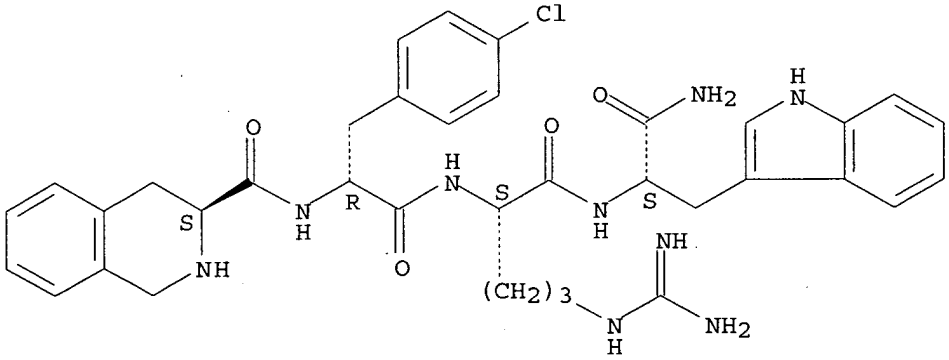
RN 869789-57-1 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-2-fluoro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



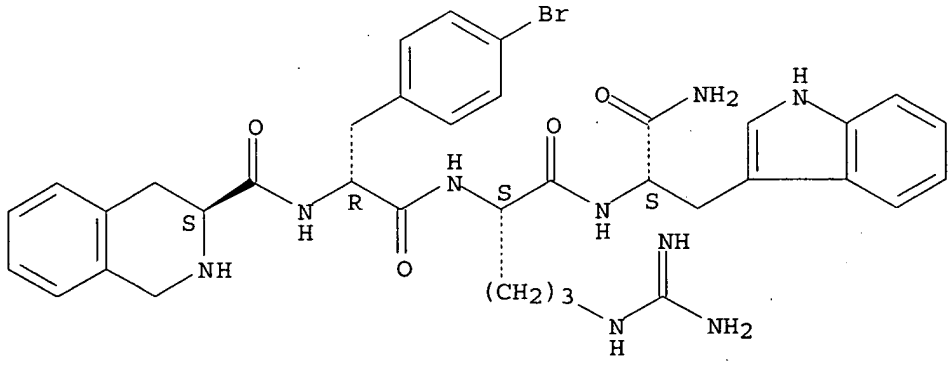
RN 869789-58-2 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 869789-59-3 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-bromo-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

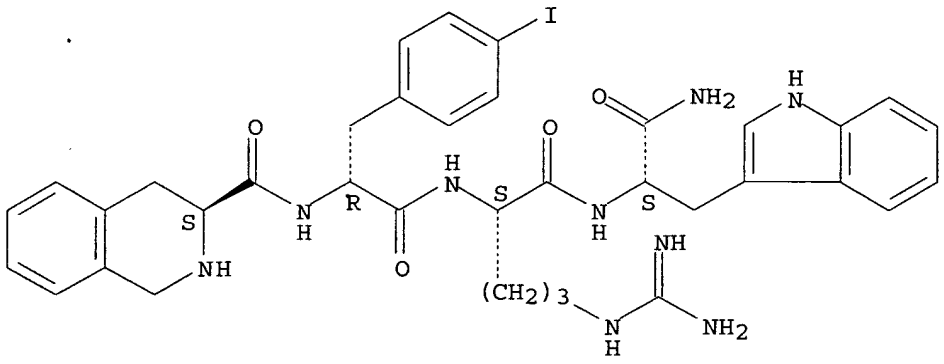
Absolute stereochemistry.



RN 869789-60-6 HCAPLUS

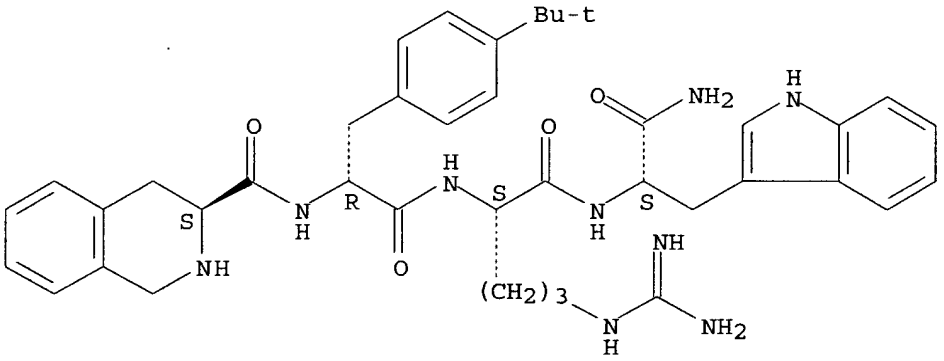
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-iodo-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



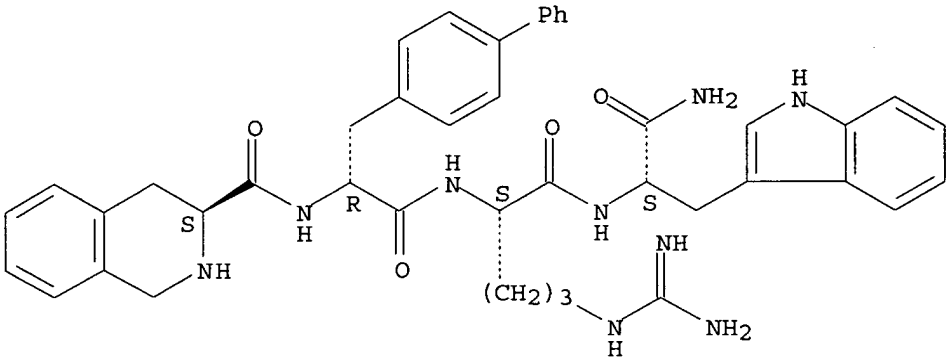
RN 869789-61-7 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-(1,1-dimethylethyl)-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



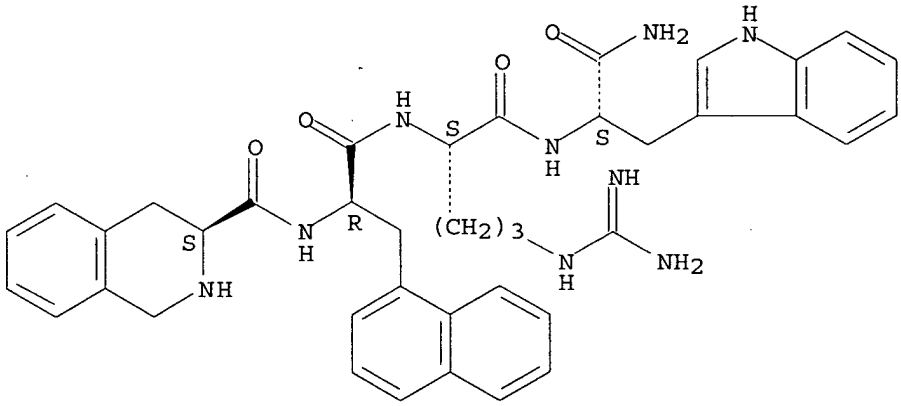
RN 869789-62-8 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-3-[1,1'-biphenyl]-4-yl-D-alanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



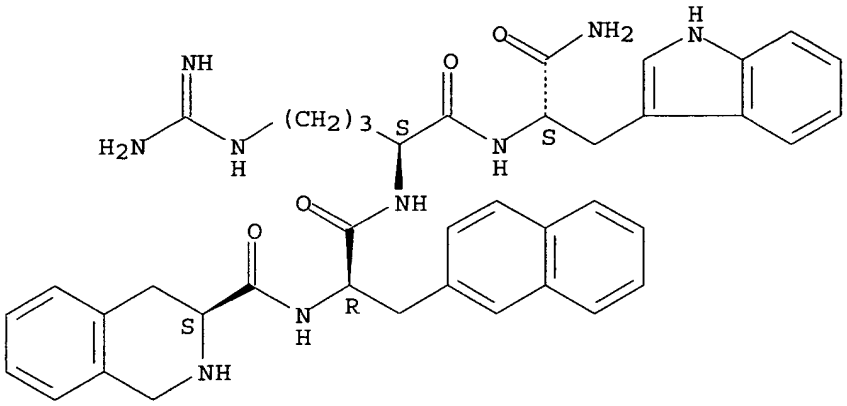
RN 869789-63-9 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-3-(1-naphthalenyl)-D-alanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 869789-64-0 HCAPLUS
CN L-Tryptophanamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-3-(2-naphthalenyl)-D-alanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1026482 HCAPLUS
DOCUMENT NUMBER: 143:301337
TITLE: Compounds providing detectable lanthanide ion complexes upon cleavage and methods for determining substrate specificity of hydrolytic enzymes
INVENTOR(S): Barrios, Amy M.; Craik, Charles S.
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S. Pat. Appl. Publ., 31 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005207981	A1	20050922	US 2004-989590		20041115
PRIORITY APPLN. INFO.:			US 2003-519938P	P	20031114

OTHER SOURCE(S): MARPAT 143:301337

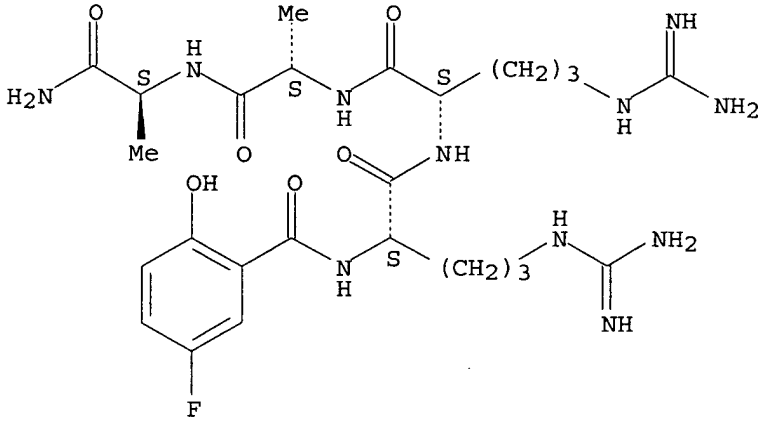
AB The present invention relates to a novel compound comprising a detectable moiety covalently linked to a structural moiety. Upon cleavage of the covalent bond linking the two moieties, the detectable moiety becomes capable of complexing a lanthanide ion, and the lanthanide-detectable moiety complex provides a detectable signal. The structural moiety of the compound is a homo- or hetero-multimer of amino acids, nucleotides, or saccharides. The detectable moiety may be salicylic acid or 1,10-phenanthroline-2-carboxylic acid derivs. A library comprising at least two member compds. with different structural moieties is also provided in this application. Further described are methods for identifying the substrate specificity of a hydrolytic enzyme by using the library of the present invention to determine the preferred structural moiety for any particular enzyme having the potential capability of cleaving the covalent bond between the detectable moiety and the structural moiety of the member compds., as well as methods for using the novel compound of this invention for detecting in a sample the presence of a pre-determined hydrolytic enzyme, whose preferred substrate specificity is known and represented by the structural moiety of the compound Thus, libraries of tetrapeptides attached to 1,10-phenanthroline-2-carboxylic acid or to

5-fluoro-2-hydroxybenzoic acid were used to identify substrates for bovine α-chymotrypsin.

IT **864656-09-7 864656-11-1**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses) (compds. providing detectable lanthanide ion complexes upon cleavage and methods for determining substrate specificity of hydrolytic enzymes)

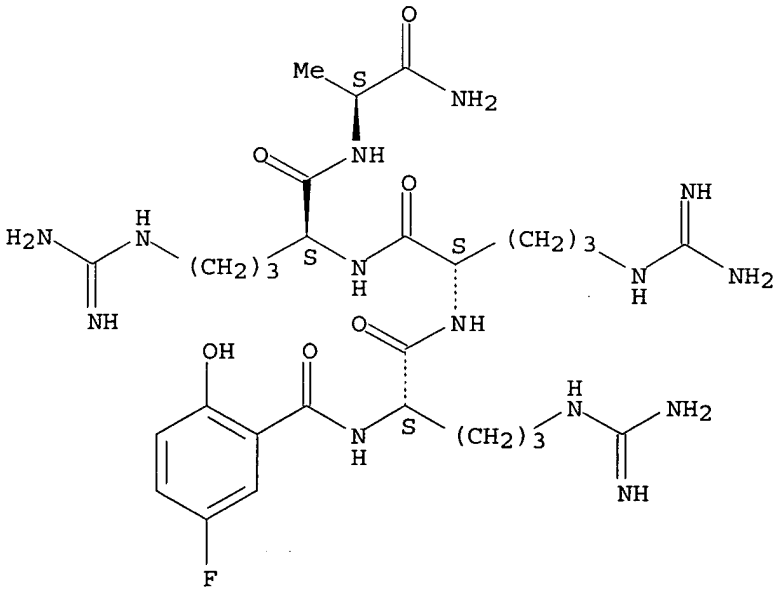
RN 864656-09-7 HCAPLUS
CN L-Alaninamide, N2-(5-fluoro-2-hydroxybenzoyl)-L-arginyl-L-arginyl-L-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 864656-11-1 HCAPLUS
CN L-Alaninamide, N2-(5-fluoro-2-hydroxybenzoyl)-L-arginyl-L-arginyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:641844 HCAPLUS
DOCUMENT NUMBER: 143:146697
TITLE: Peptidic mediators of reverse cholesterol transport for the treatment of hypercholesterolemia
INVENTOR(S): Sircar, Jagadish C.; Alisala, Kashinatham; Nikoulin, Igor
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 137 pp., Cont.-in-part of U.S. Ser. No. 829,855.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005159362	A1	20050721	US 2004-975157		20041027
PRIORITY APPLN. INFO.:			US 2003-464667P	P	20030422
			US 2004-829855	A2	20040422

OTHER SOURCE(S): MARPAT 143:146697

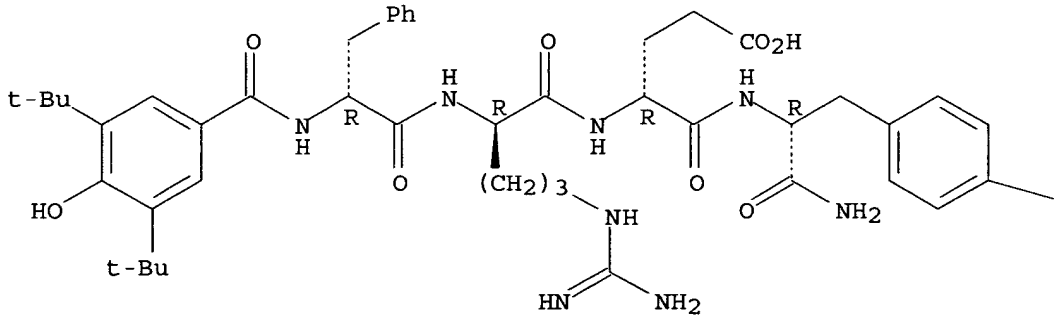
AB The invention provides compns. adapted to enhance reverse cholesterol transport in mammals. The compns. are suitable for oral delivery and useful in the treatment and/or prevention of disease conditions associated with hypercholesterolemia. Compds. of the invention include a variety of peptide/peptidomimetic compds.

IT **786691-63-2 786691-64-3 786691-70-1 786691-81-4 786691-82-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidomimetic mediators of reverse cholesterol transport for treatment of hypercholesterolemia)

RN 786691-63-2 HCAPLUS
CN D-Tyrosinamide, N-[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzoyl]-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

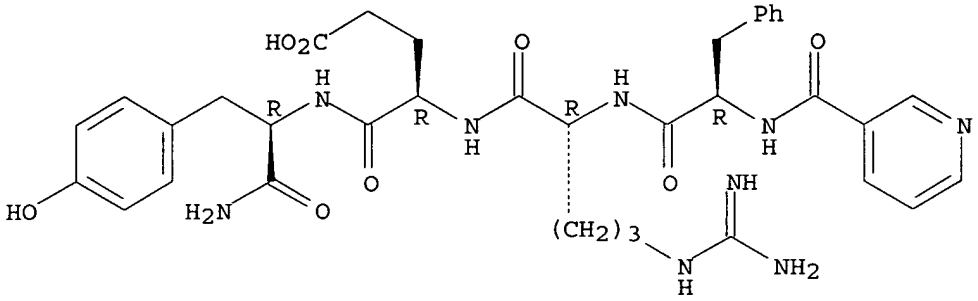
PAGE 1-A



—OH

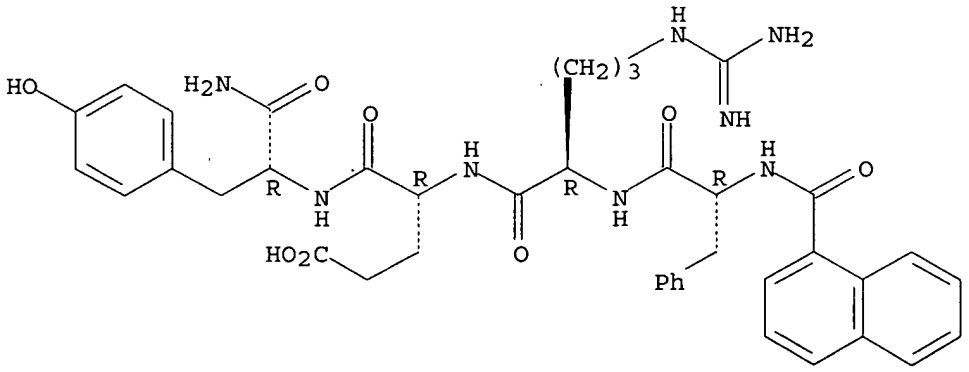
RN 786691-64-3 HCAPLUS
CN D-Tyrosinamide, N-(3-pyridinylcarbonyl)-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



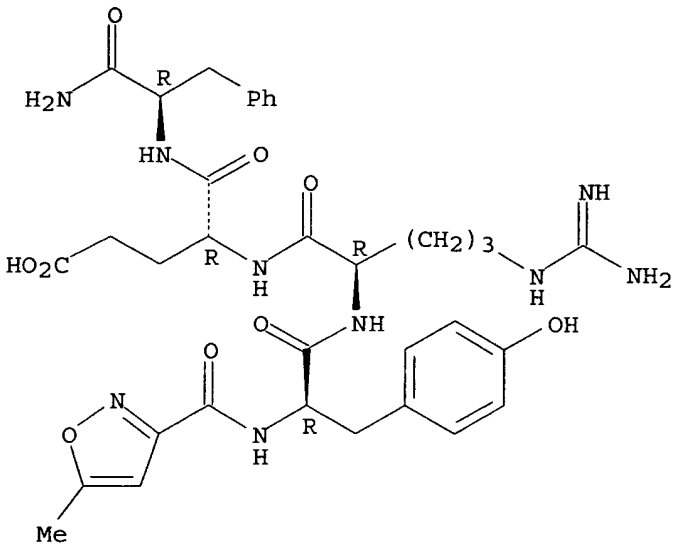
RN 786691-70-1 HCAPLUS
CN D-Tyrosinamide, N-(1-naphthalenylcarbonyl)-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



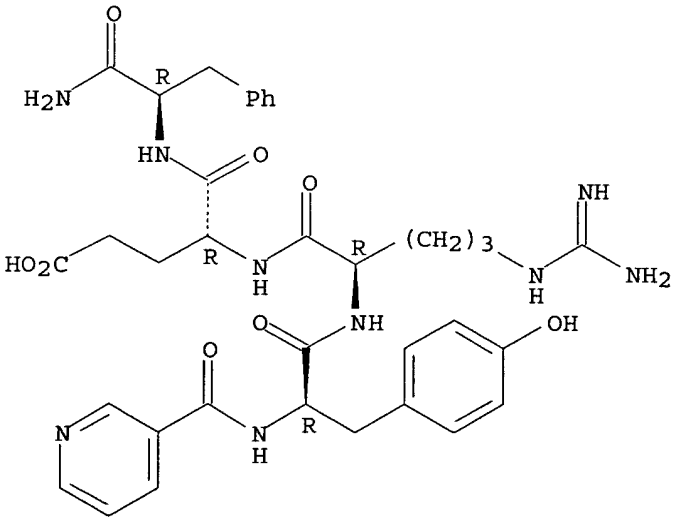
RN 786691-81-4 HCAPLUS
CN D-Phenylalaninamide, N-[(5-methyl-3-isoxazolyl)carbonyl]-D-tyrosyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 786691-82-5 HCAPLUS
CN D-Phenylalaninamide, N-(3-pyridinylcarbonyl)-D-tyrosyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



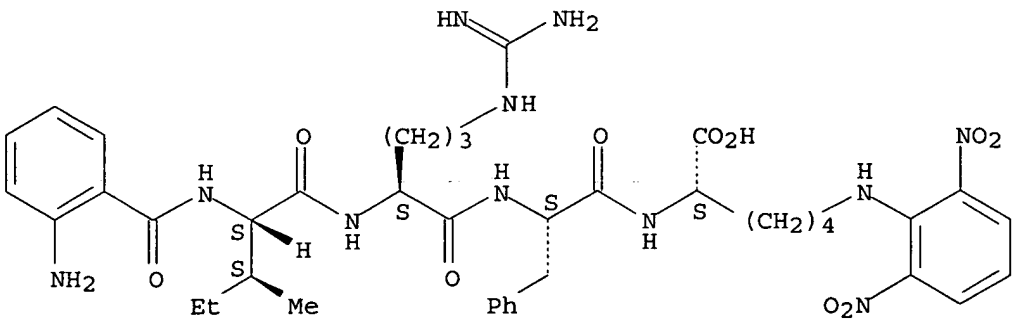
L12 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:999732 HCAPLUS
DOCUMENT NUMBER: 142:129615
TITLE: Positional-Scanning Combinatorial Libraries of Fluorescence Resonance Energy Transfer Peptides for Defining Substrate Specificity of the Angiotensin I-Converting Enzyme and Development of Selective C-Domain Substrates
AUTHOR(S): Bersanetti, Patricia A.; Andrade, Maria Claudina C.;

Casarini, Dulce E.; Juliano, Maria A.; Nchinda, Aloysius T.; Sturrock, Edward D.; Juliano, Luiz; Carmona, Adriana K.
CORPORATE SOURCE: Department of Biophysics and Department of Medicine, Division of Nephrology, Escola Paulista de Medicina, Universidade Federal de Sao Paulo, Sao Paulo, 04044-020, Brazil
SOURCE: Biochemistry (2004), 43(50), 15729-15736
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Positional-scanning combinatorial libraries of fluorescence resonance energy transfer peptides were used for the analyses of the S3 to S1' subsites of the somatic angiotensin I-converting enzyme (ACE). Substrate specificity of ACE catalytic domains (C- and N-domains) was assessed in an effort to design selective substrates for the C-domain. Initially, we defined the S1 specificity by preparing a library with the general structure Abz-GXXZXK(Dnp)-OH [Abz = o-aminobenzoic acid, K(Dnp) = Nε-2,4-dinitrophenyllysine, and X is a random residue], where Z was successively occupied with one of the 19 natural amino acids with the exception of Cys. The peptides containing Arg and Leu in the P1 position had higher C-domain selectivity. In the sublibraries Abz-GXXRZK(Dnp)-OH, Abz-GXZRXK(Dnp)-OH, and Abz-GZXRXK(Dnp)-OH, Arg was fixed at P1 so we could define the C-domain selectivity of the S1', S2, and S3 subsites. On the basis of the results from these libraries, we synthesized peptides Abz-GVIRFK(Dnp)-OH and Abz-GVILFK(Dnp)-OH which contain the most favorable residues for C-domain selectivity. Systematic reduction of the length of these two peptides resulted in Abz-LFK(Dnp)-OH, which demonstrated the highest selectivity for the recombinant ACE C-domain (kcat/Km = 36.7 μM-1 s-1) vs. the N-domain (kcat/Km = 0.51 μM-1 s-1). The substrate binding of Abz-LFK(Dnp)-OH with testis ACE using a combination of conformational anal. and mol. docking was examined, and the results shed new light on the binding characteristics of the enzyme.

IT **826995-48-6P**
RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation); PRP (Properties); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation)
(positional-scanning combinatorial libraries of fluorescence resonance energy transfer peptides for defining substrate specificity of angiotensin I-converting enzyme and development of selective C-domain substrates)

RN 826995-48-6 HCAPLUS
CN L-Lysine, N-(2-aminobenzoyl)-L-isoleucyl-L-arginyl-L-phenylalanyl-N6-(2,6-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:927246 HCAPLUS
DOCUMENT NUMBER: 141:388716
TITLE: Mediators of reverse cholesterol transport for the treatment of hypercholesterolemia
INVENTOR(S): Sircar, Jagadish C.; Alisala, Kashinatham; Nikoulin, Igor
PATENT ASSIGNEE(S): Avanir Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 181 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004094471	A2	20041104	WO 2004-US12445	20040422
WO 2004094471	A3	20050616		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2522758	AA	20041104	CA 2004-2522758	20040422
EP 1615954	A2	20060118	EP 2004-760126	20040422
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				

PRIORITY APPLN. INFO.: US 2003-464667P P 20030422
WO 2004-US12445 W 20040422

OTHER SOURCE(S): MARPAT 141:388716

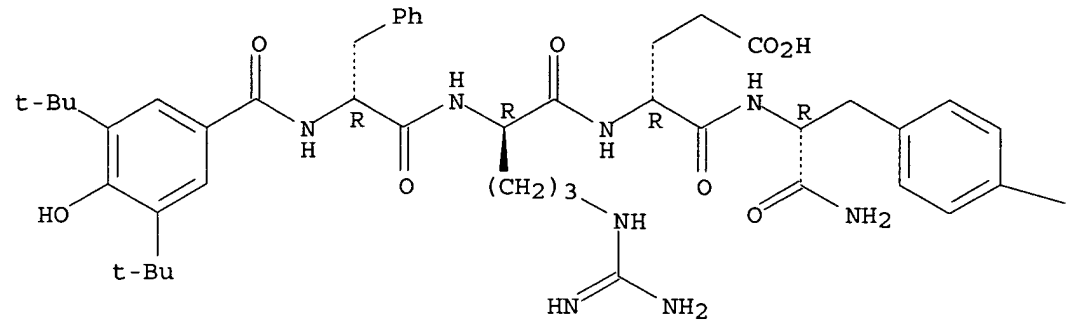
AB The present invention provides compns. adapted to enhance reverse cholesterol transport in mammals. The compns. are suitable for oral delivery and useful in the treatment and/or prevention of hypercholesterolemia, atherosclerosis and associated cardiovascular diseases.

IT **786691-63-2 786691-64-3 786691-70-1**
786691-81-4 786691-82-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mediators of reverse cholesterol transport for treatment of hypercholesterolemia and atherosclerosis by affecting lipoprotein cholesterol in relation to drug screening)

RN 786691-63-2 HCAPLUS
CN D-Tyrosinamide, N-[3,5-bis(1,1-dimethylethyl)-4-hydroxybenzoyl]-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

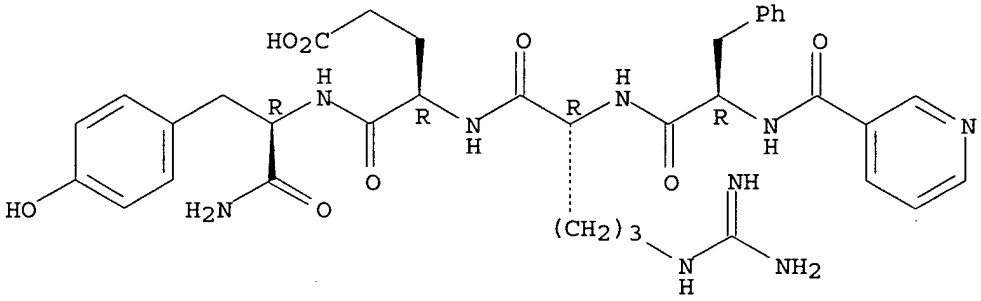


PAGE 1-B

—OH

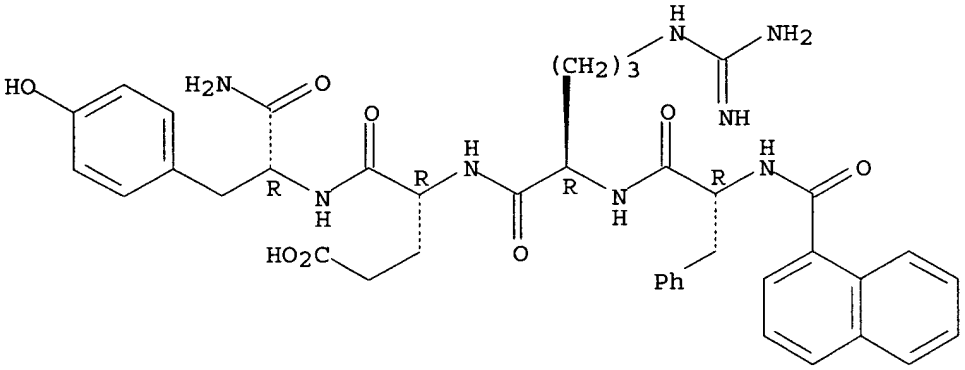
RN 786691-64-3 HCAPLUS
CN D-Tyrosinamide, N-(3-pyridinylcarbonyl)-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



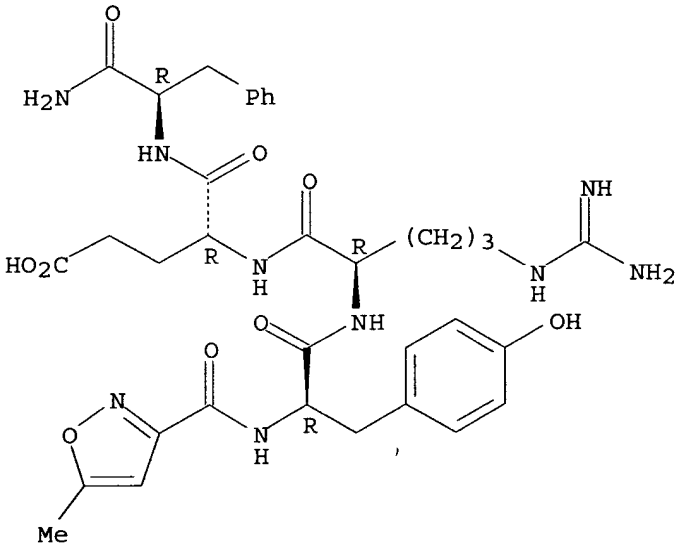
RN 786691-70-1 HCAPLUS
CN D-Tyrosinamide, N-(1-naphthalenylcarbonyl)-D-phenylalanyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 786691-81-4 HCAPLUS
CN D-Phenylalaninamide, N-[(5-methyl-3-isoxazolyl)carbonyl]-D-tyrosyl-D-arginyl-D-α-glutamyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 786691-82-5 HCAPLUS
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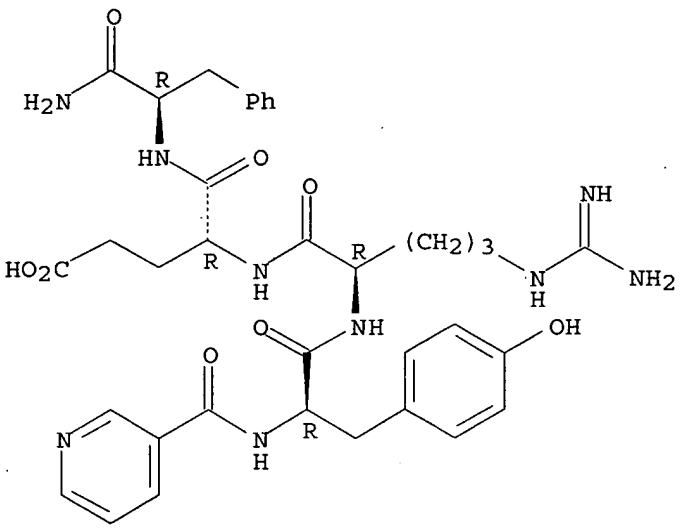
Absolute stereochemistry.



L12 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:781509 HCAPLUS
DOCUMENT NUMBER: 142:34412
TITLE: Differences in substrate specificities between cysteine protease CPB isoforms of Leishmania mexicana are mediated by a few amino acid changes
AUTHOR(S): Juliano, Maria A.; Brooks, Darren R.; Selzer, Paul M.; Pandolfo, Hector L.; Judice, Wagner A. S.; Juliano, Luiz; Meldal, Morten; Sanderson, Sanya J.; Mottram, Jeremy C.; Coombs, Graham H.
CORPORATE SOURCE: Department of Biophysics, Escola Paulista de Medicina, Universidade Federal de Sao Paulo, Brazil
SOURCE: European Journal of Biochemistry (2004), 271(18), 3704-3714
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The CPB genes of the protozoan parasite Leishmania mexicana encode stage-regulated cathepsin L-like cysteine proteases that are important virulence factors and are in a tandem array of 19 genes. In this study, we have compared the substrate preferences of two CPB isoforms, CPB2.8 and CPB3, and a H84Y mutant of the latter enzyme, to analyze the roles played by the few amino acid differences between the isoenzymes in determining substrate specificity. CPB3 differs from CPB2.8 at just three residues (N60D, D61N and D64S) in the mature domain. The H84Y mutation mimics an addnl. change present in another isoenzyme, CPB18. The active recombinant CPB isoenzymes and mutant were produced using Escherichia coli and the S1-S3 and S1'-S3' subsite specificities determined using a series of fluorogenic peptide derivs. in which substitutions were made on positions P3 to P3' by natural amino acids. Carboxydipeptidase activities of CPB3 and H84Y were also observed using the peptide Abz-FRAK(Dnp)-OH and some of its analogs. The kinetic parameters of hydrolysis by CPB3, H84Y and CPB2.8 of the synthetic substrates indicates that the specificity of S3 to S3' subsites is influenced greatly by the modifications at amino acids 60, 61, 64 and 84. Particularly noteworthy was the large preference for Pro in the P2' position for the hydrolytic activity of CPB3, which may be

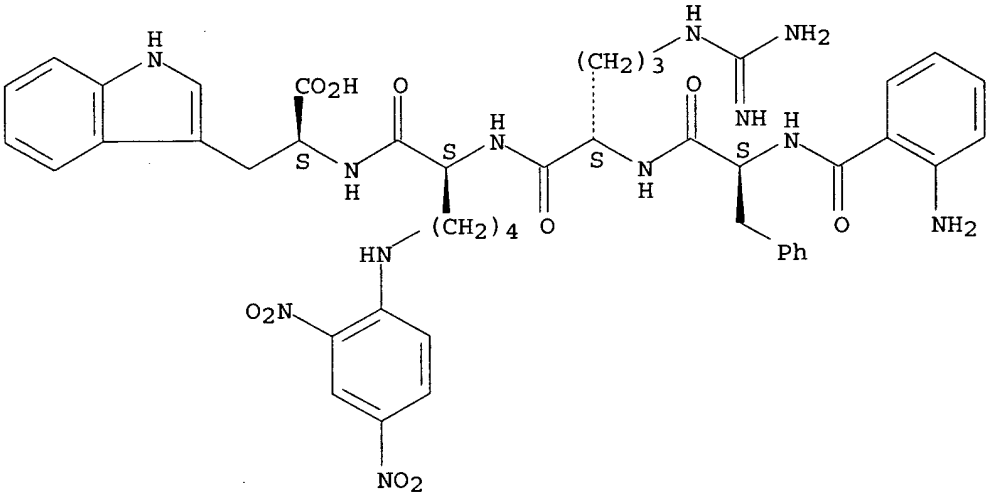
relevant to a role in the activation mechanism of the L. mexicana CPBs.

IT **500799-60-0 500799-62-2 500799-63-3**
685144-20-1 685144-22-3
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(carboxydipeptidase activity specificity; differences in substrate specificities between cysteine proteinase CPB isoforms of Leishmania mexicana are mediated by a few amino acid changes)

RN 500799-60-0 HCAPLUS

CN L-Tryptophan, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-N6-(2,4-dinitrophenyl)-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

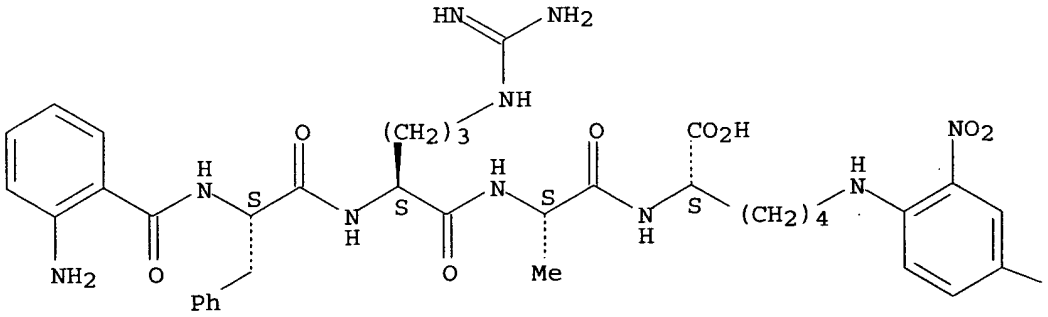


RN 500799-62-2 HCAPLUS

CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-alanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



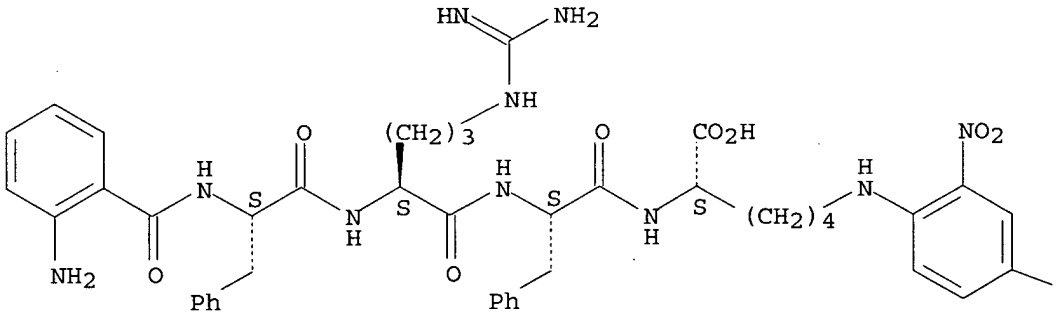
PAGE 1-B

NO_2

RN 500799-63-3 HCAPLUS
CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-phenylalanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



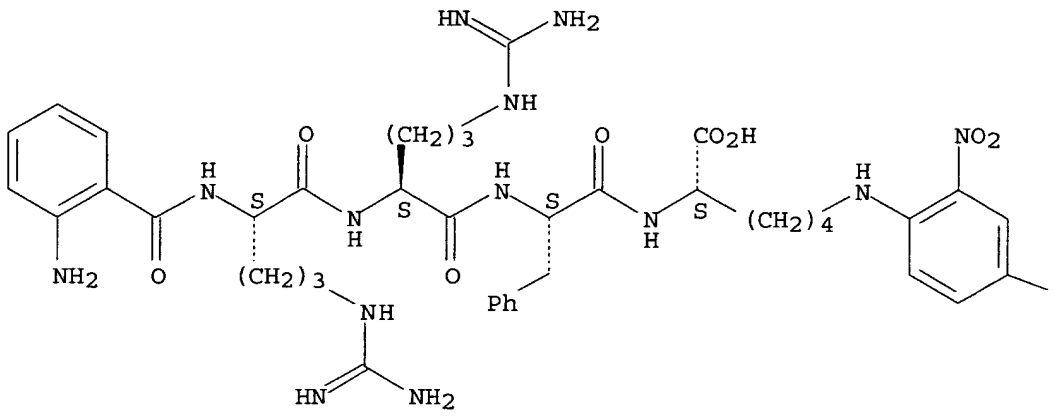
PAGE 1-B

NO_2

RN 685144-20-1 HCAPLUS
CN L-Lysine, N2-(2-aminobenzoyl)-L-arginyl-L-arginyl-L-phenylalanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

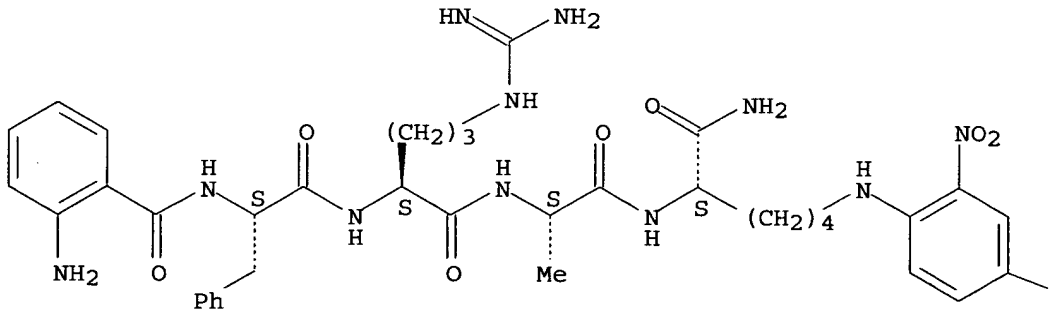


PAGE 1-B

RN 685144-22-3 HCAPLUS
CN L-Lysinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-alanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

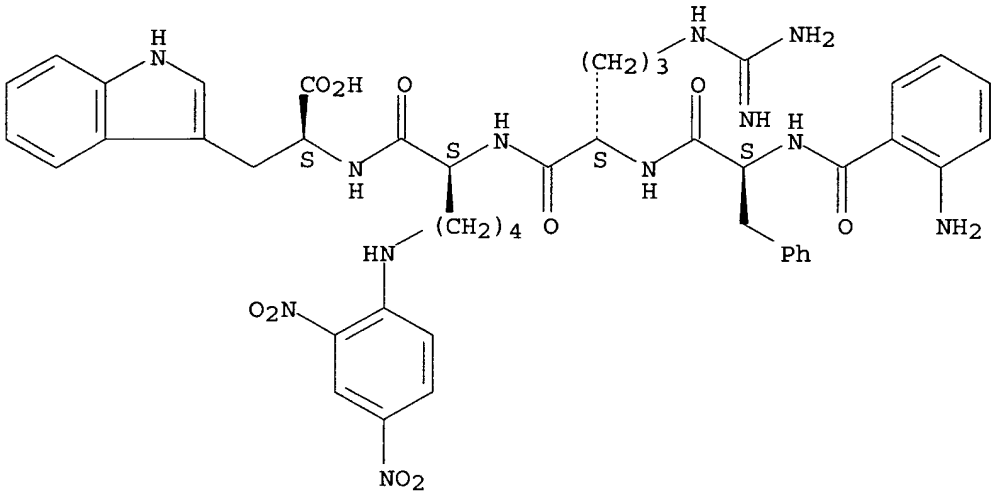
L12 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:201913 HCAPLUS
DOCUMENT NUMBER: 140:370668
TITLE: Carboxydipeptidase activities of recombinant cysteine peptidases: cruzain of Trypanosoma cruzi and CPB of Leishmania mexicana
AUTHOR(S): Judice, Wagner A. S.; Puzer, Luciano; Cotrin, Simone S.; Carmona, Adriana K.; Coombs, Graham H.; Juliano, Luiz; Juliano, Maria A.
CORPORATE SOURCE: Department of Biophysics, Escola Paulista de Medicina, Universidade Federal de Sao Paulo, Sao Paulo, 04044-20, Brazil
SOURCE: European Journal of Biochemistry (2004), 271(5), 1046-1053
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The recombinant cysteine peptidases, cruzain from Trypanosoma cruzi and CPB2.8ΔCTE from Leishmania mexicana, are cathepsin L-like and characteristically endopeptidases. In this study, we characterized the carboxydi-peptidase activities of these enzymes and compared them with those of human recombinant cathepsin B and cathepsin L. The anal. used the internally quenched fluorescent peptide Abz-FRFK*-OH and some of its analogs, where Abz is ortho-aminobenzoic acid and K* is (2,4-dinitrophenyl)-ε-NH2-lysine. These peptides were demonstrated to be very sensitive substrates, due to the strong quenching effect of K* on the fluorescence of the Abz group. The carboxy-dipeptidase activity of cruzain was shown to be very similar to that of cathepsin B, while that of CPB2.8ΔCTE is closer to the carboxydipeptidase activity of cathepsin L. The S2 subsite architecture of cruzain and the nature of the amino acid at the P2 position of the substrates determine its carboxydipeptidase activity and gives further and direct support to the notion that the carboxydipeptidase activity of the papain family cysteine peptidases rely on the S2-P2 interaction. Cruzain and CPB2.8ΔCTE presented a broad pH-range for both the endo- and exo-peptidase activities, although the later is approx. one order of magnitude lower. This feature, that is not common in related mammalian cysteine peptidases, is consistent with the enzymes being exposed to different environmental conditions and having different locations during parasite development.

IT **500799-60-0 500799-62-2 500799-63-3**
685144-20-1 685144-22-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(carboxydipeptidase activities of cruzain of Trypanosoma cruzi, CPB of Leishmania mexicana, cathepsin L and cathepsin B)

RN 500799-60-0 HCAPLUS
CN L-Tryptophan, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-N6-(2,4-dinitrophenyl)-L-lysyl- (9CI) (CA INDEX NAME)

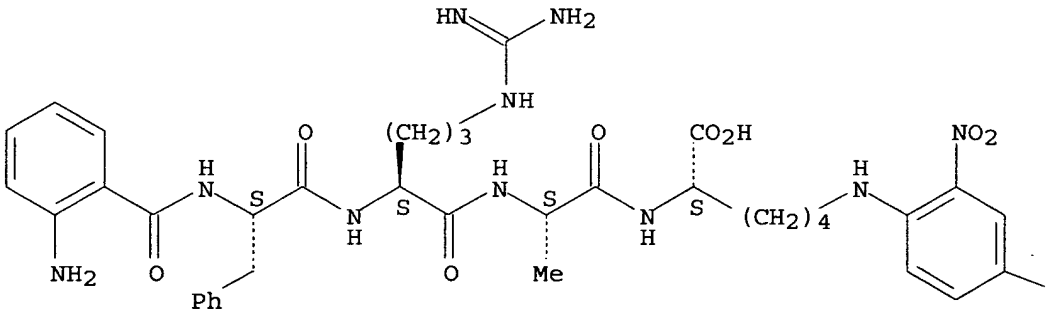
Absolute stereochemistry.



RN 500799-62-2 HCAPLUS
CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-alanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



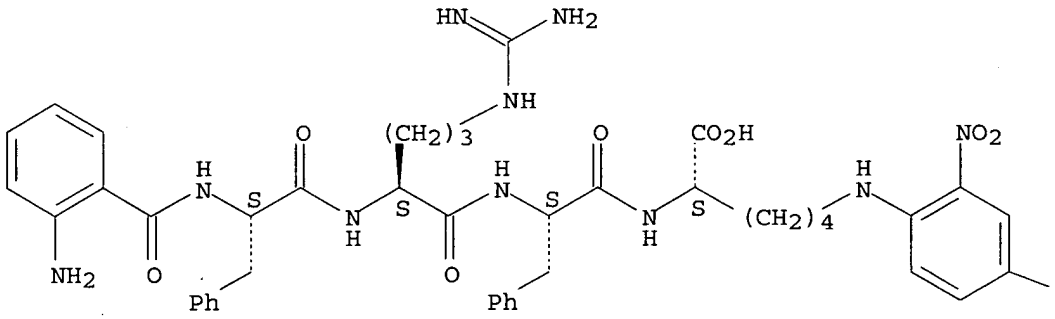
PAGE 1-B

NO_2

RN 500799-63-3 HCAPLUS
CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-phenylalanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



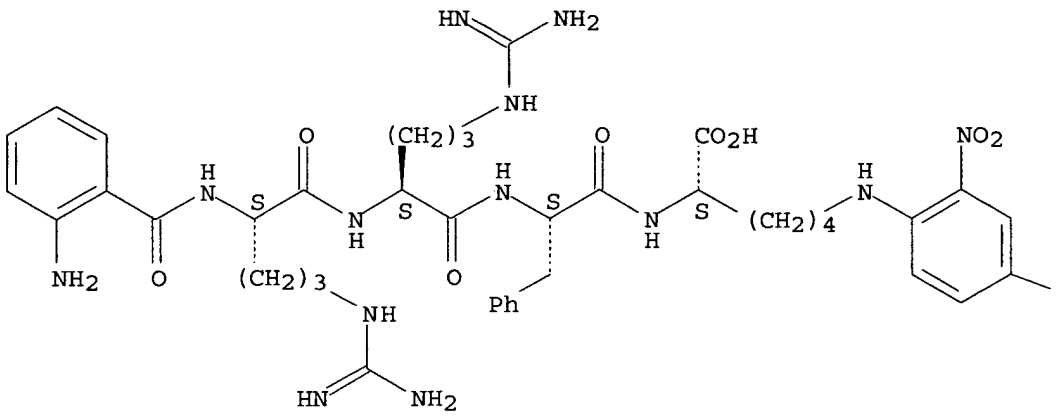
PAGE 1-B

NO_2

RN 685144-20-1 HCAPLUS
CN L-Lysine, N2-(2-aminobenzoyl)-L-arginyl-L-arginyl-L-phenylalanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

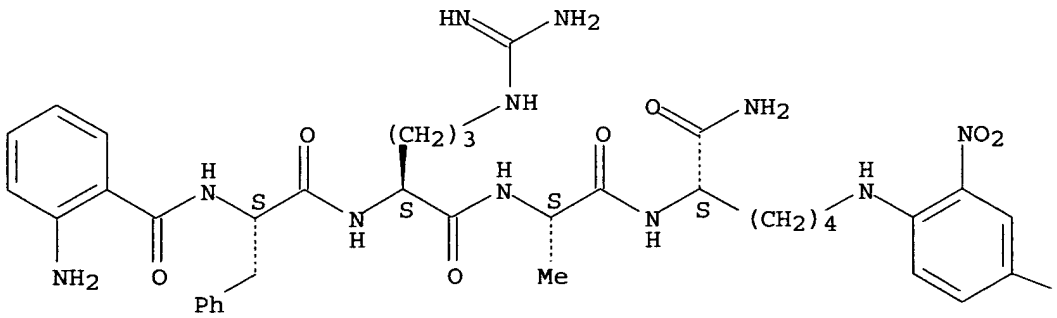


PAGE 1-B

RN 685144-22-3 HCAPLUS
CN L-Lysinamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-alanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:435053 HCAPLUS
DOCUMENT NUMBER: 139:12393
TITLE: Stabilization of radiopharmaceutical compositions using hydrophilic 6-hydroxychromans
INVENTOR(S): Cyr, John E.
PATENT ASSIGNEE(S): Diatide, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of Appl. No. PCT/US01/50423.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003103899	A1	20030605	US 2002-131346	20020424
US 6881396	B2	20050419		
WO 2002060491	A2	20020808	WO 2001-US50423	20011024
WO 2002060491	A3	20031106		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005207973	A1	20050922	US 2005-86966	20050322

PRIORITY APPLN. INFO.:

US 2000-695360	A2 20001024
WO 2001-US50423	A2 20011024
US 2000-694992	A1 20001024
US 2000-695494	A1 20001024
US 2002-131346	A3 20020424

OTHER SOURCE(S): MARPAT 139:12393
AB A composition comprising a peptide or non-peptide radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxychroman derivative, e.g., 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox), is

described. A kit comprising a sealed vial containing a predetd. quantity of a radiopharmaceutical precursor and a stabilizing amount of a hydrophilic 6-hydroxychroman derivative is also described. For example, Trolox increased the radiolabeling yield and the stability of 99mTc depreotide prepared from the kit.

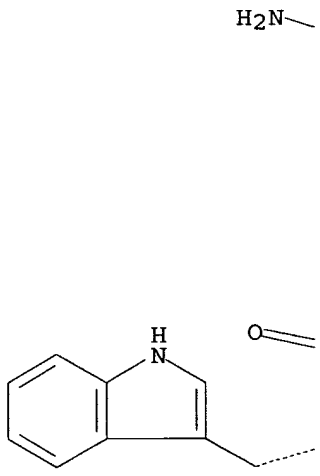
IT **161982-53-2 445311-66-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilization of radiopharmaceutical precursors by hydrophilic hydroxychromans)

RN 161982-53-2 HCAPLUS

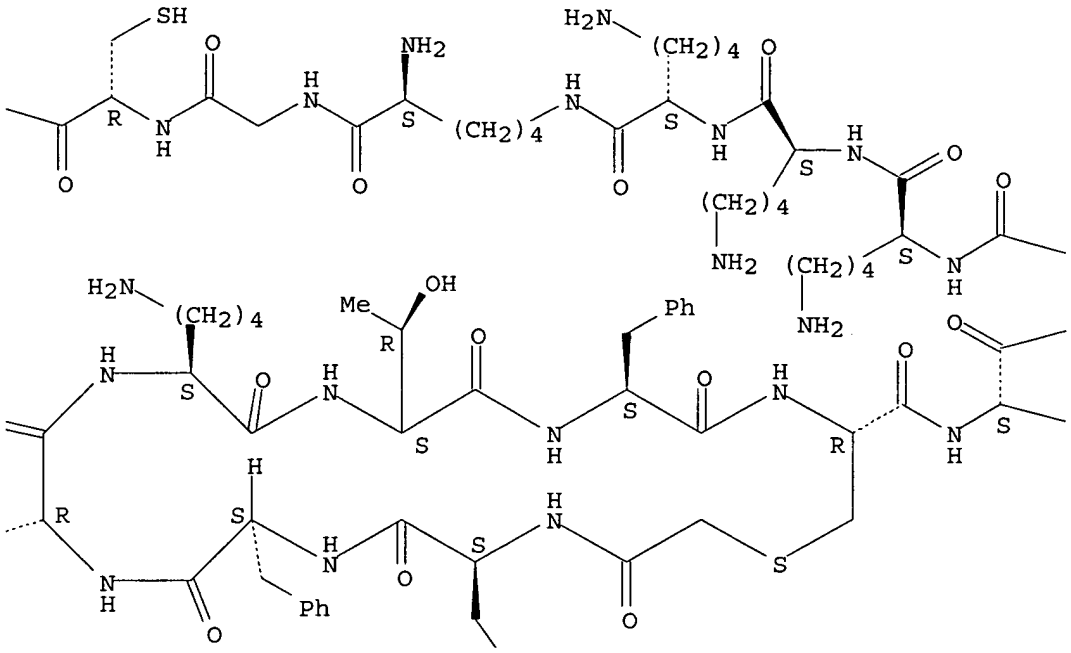
CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

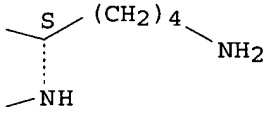
PAGE 1-A

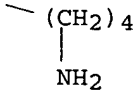


PAGE 1-B



PAGE 1-C





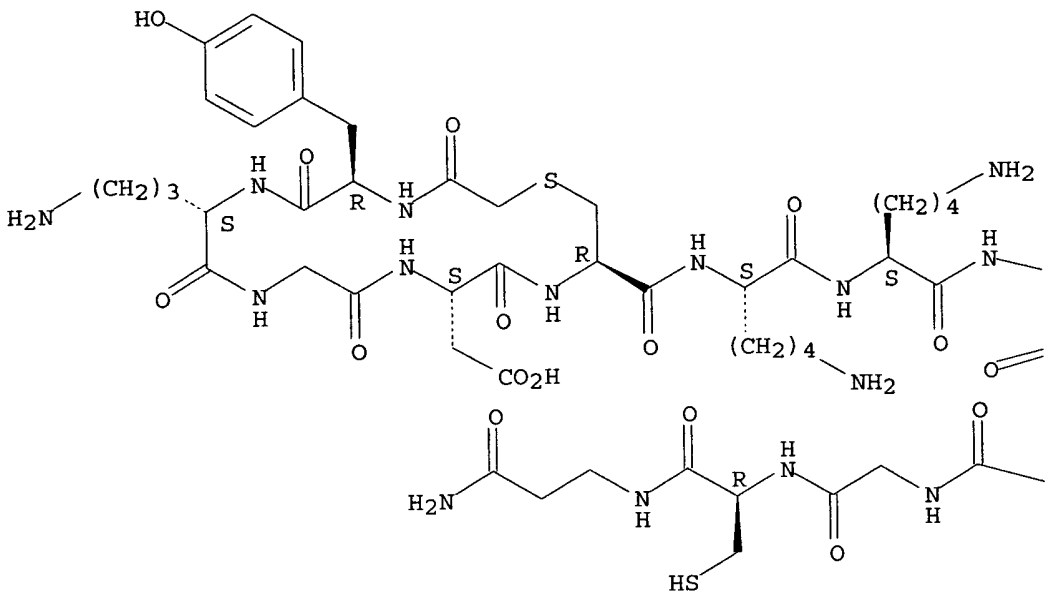
PAGE 2-B

RN 445311-66-0 HCAPLUS

CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-L-ornithylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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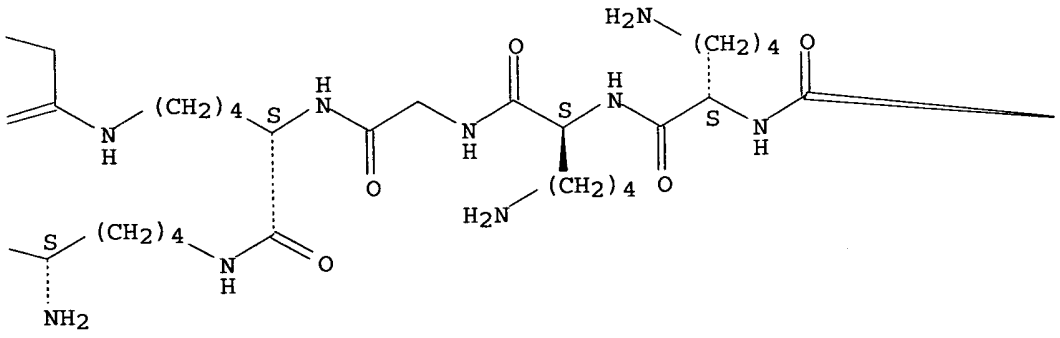
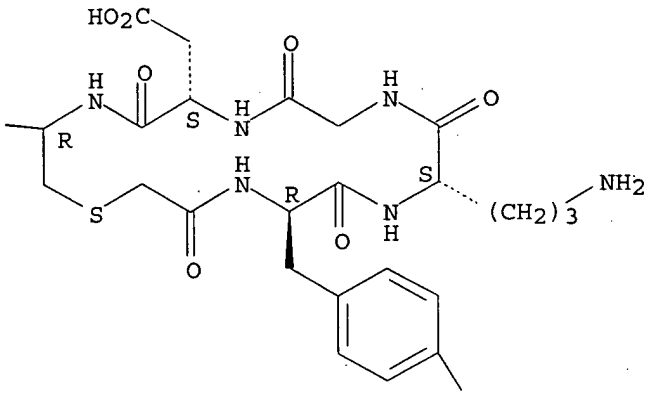


PAGE 1-C



PAGE 2-C

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:435052 HCAPLUS
DOCUMENT NUMBER: 139:12392
TITLE: Stabilization of radiopharmaceutical compositions using hydrophilic thioethers and hydrophilic 6-hydroxychromans
INVENTOR(S): Cyr, John E.; Pearson, Daniel A.
PATENT ASSIGNEE(S): Diatide, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of Appl. No. PCT/US01/50423.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003103895	A1	20030605	US 2002-131546	20020424
US 6989138	B2	20060124		
WO 2002060491	A2	20020808	WO 2001-US50423	20011024
WO 2002060491	A3	20031106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2000-695494	A2 20001024
WO 2001-US50423	A2 20011024
US 2000-694992	A1 20001024
US 2000-695360	A1 20001024

OTHER SOURCE(S): MARPAT 139:12392

AB A composition containing a peptide or non-peptide radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxychroman derivative is described. The thioether is selected from, e.g., methionine, ethionine, 3-(methylthio)propionaldehyde, 2-(ethylthio)ethylamine, buthionine, S-methyl-cysteine, and methioninol. The hydrophilic 6-hydroxychroman used is, e.g., 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid or 6-hydroxy-2,5,7,8-tetramethylchroman-2-glucosamine. A kit comprising a sealed vial containing a predetd. quantity of a radiopharmaceutical precursor and a stabilizing amount of a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxychroman derivative is also described. For example, the combination of L-methionine and Trolox increased the radiolabeling yield and the stability of 99mTc depreotide prepared from the kit.

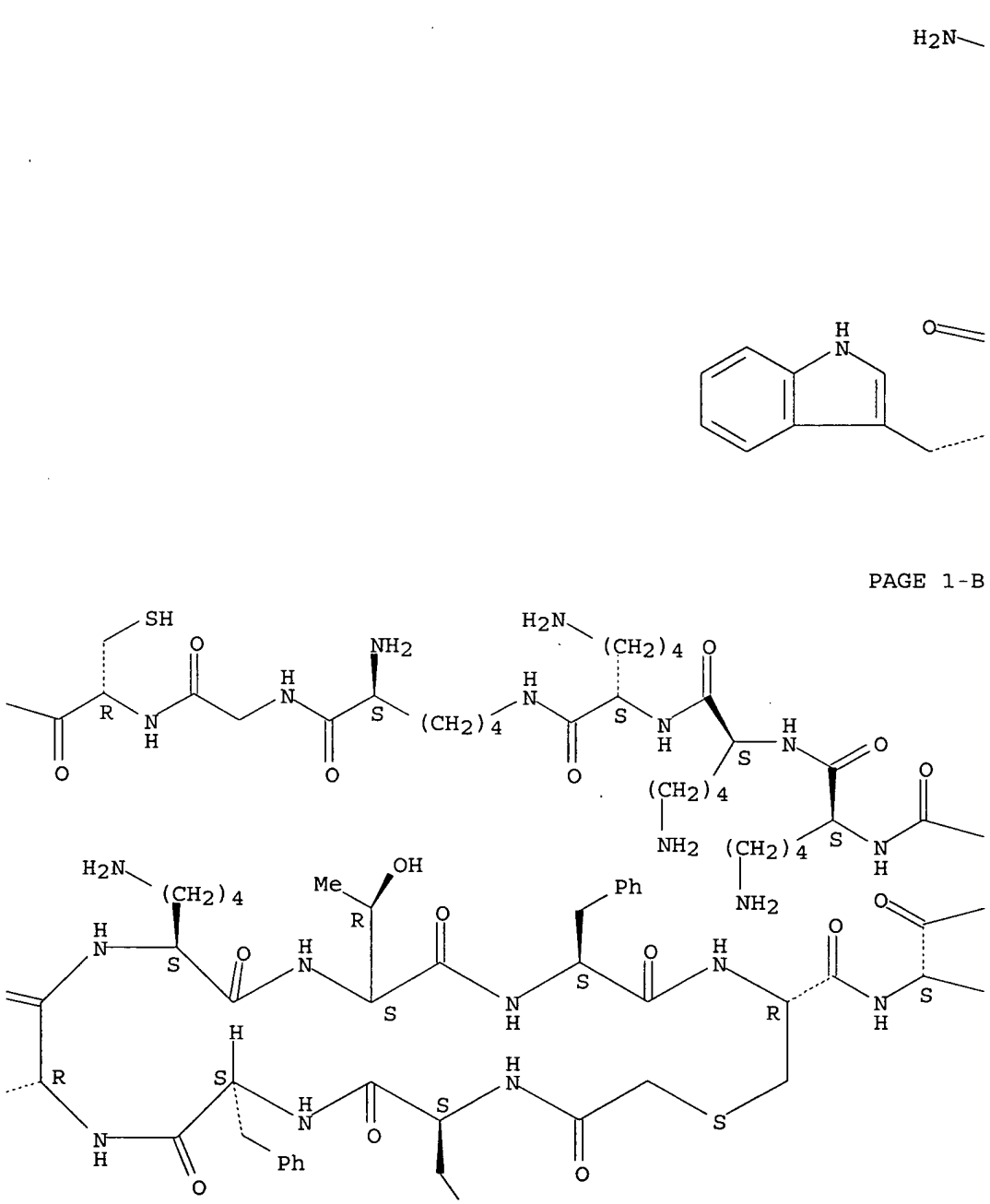
IT **161982-53-2 445311-66-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilization of radiopharmaceutical precursors by hydrophilic thioethers and hydrophilic 6-hydroxychromans)

RN 161982-53-2 HCAPLUS

CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

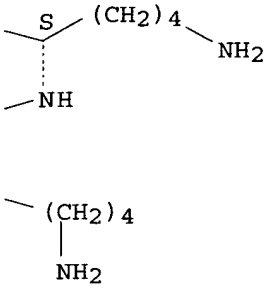
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

PAGE 1-C

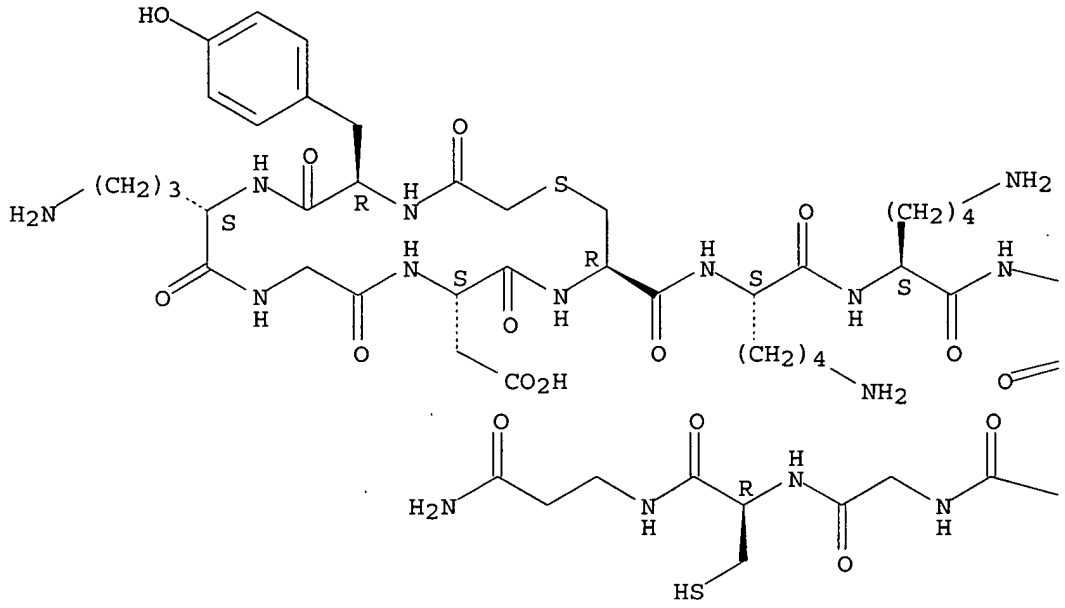


PAGE 2-B

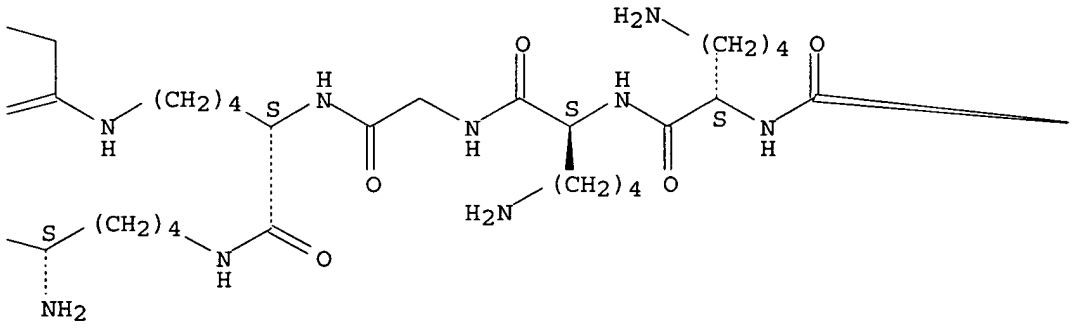
RN 445311-66-0 HCAPLUS
CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-L-ornithylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

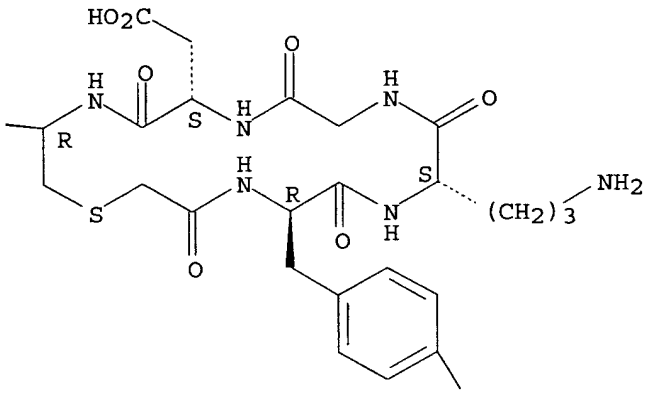
PAGE 1-A



PAGE 1-B



PAGE 1-C



PAGE 2-C

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:300424 HCAPLUS
DOCUMENT NUMBER: 138:316887
TITLE: Stabilization of radiopharmaceutical compositions using hydrophilic thioethers
INVENTOR(S): Cyr, John E.; Pearson, Daniel A.
PATENT ASSIGNEE(S): Diatide, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 19 pp., Cont.-in-part of Appl. No. PCT/US01/50423.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003072709	A1	20030417	US 2002-131543	20020424
US 6902718	B2	20050607		
WO 2002060491	A2	20020808	WO 2001-US50423	20011024
WO 2002060491	A3	20031106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,

CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT,
RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG,
KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG

US 2005180918 A1 20050818 US 2005-88596 20050324
PRIORITY APPLN. INFO.: US 2000-694992 A2 20001024
WO 2001-US50423 A2 20011024
US 2000-695360 A1 20001024
US 2000-695494 A1 20001024
US 2002-131543 A3 20020424

OTHER SOURCE(S): MARPAT 138:316887

AB Radiopharmaceutical compns. which are stabilized by addition of a hydrophilic thioether (Markush structures are included).

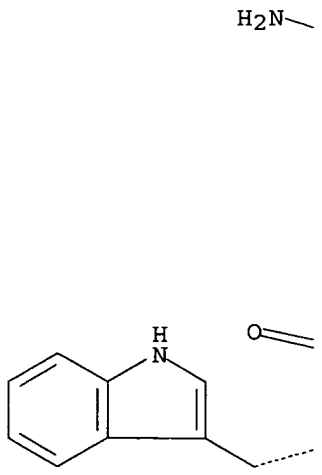
IT **161982-53-2 445311-66-0**
RL: BUU (Biological use, unclassified); CPS (Chemical process); PEP (Physical, engineering or chemical process); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(stabilization of radiopharmaceutical compns. using hydrophilic thioethers)

RN 161982-53-2 HCAPLUS

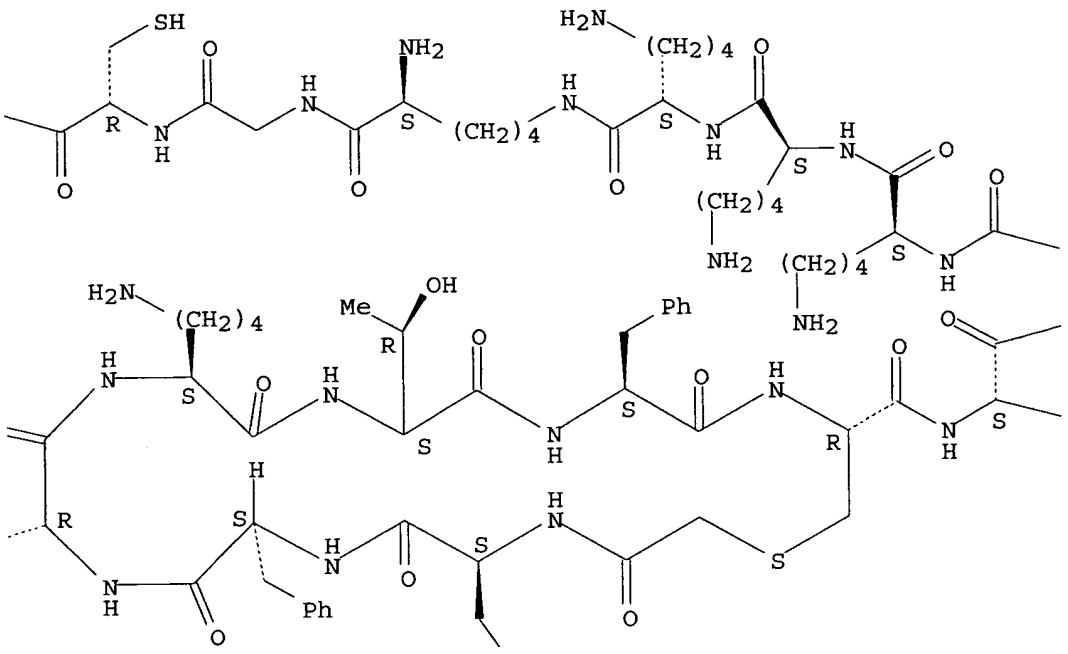
CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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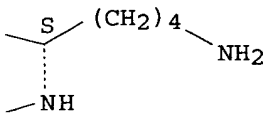
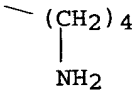




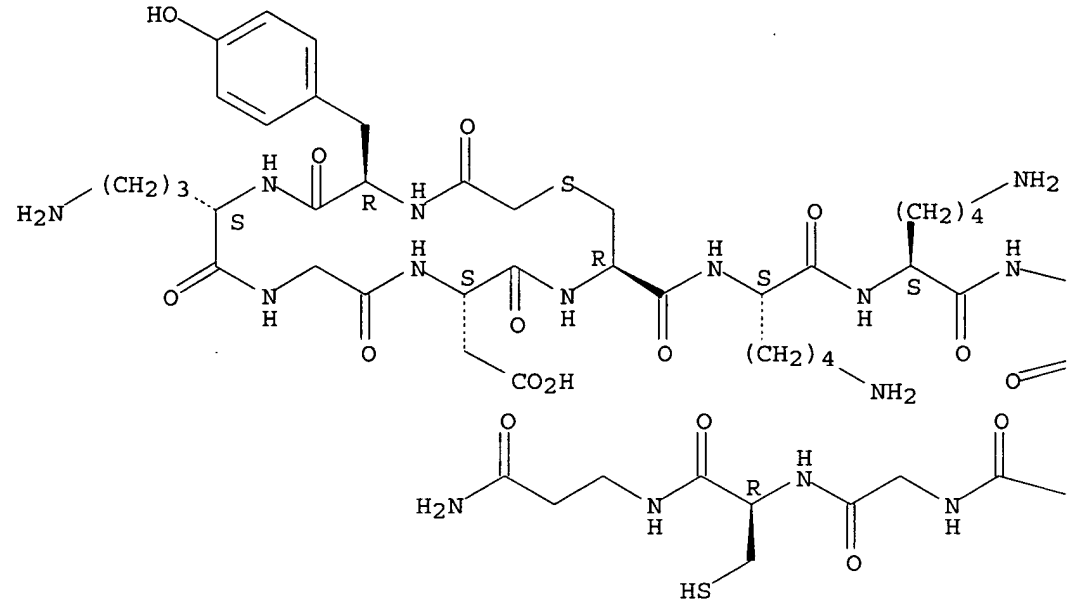
PAGE 2-B

RN 445311-66-0 HCAPLUS

CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-L-ornithylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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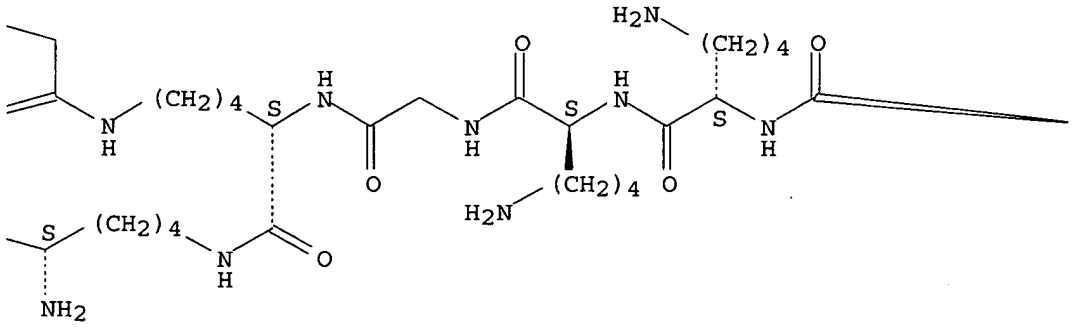

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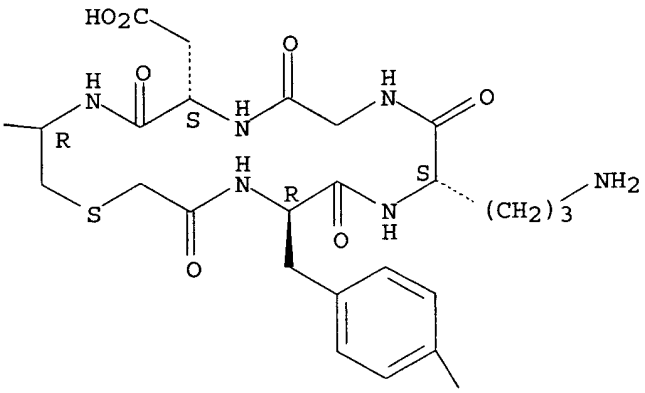


PAGE 2-C

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:58220 HCAPLUS
DOCUMENT NUMBER: 138:117676
TITLE: Linear and cyclic melanocortin receptor-specific peptides, and therapeutic use
INVENTOR(S): Sharma, Shubh D.; Shadiack, Annette M.; Yang, Wei; Rajpurohit, Ramesh
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003006620	A2	20030123	WO 2002-US22196	20020711
WO 2003006620	A3	20031127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,

RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2453515	AA	20030123	CA 2002-2453515		20020711
EP 1441750	A2	20040804	EP 2002-756458		20020711
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
JP 2004534851	T2	20041118	JP 2003-512379		20020711
US 2004138136	A1	20040715	US 2003-638071		20030808
US 2005038230	A1	20050217	US 2004-756212		20040112
US 2006014676	A1	20060119	US 2005-174845		20050705
US 2006014194	A1	20060119	US 2005-174851		20050705
PRIORITY APPLN. INFO.:			US 2001-304836P	P	20010711
			US 2000-606501	A2	20000628
			US 2002-40547	A2	20020104
			WO 2002-US22196	W	20020711
			US 2003-638071	A2	20030808
			US 2004-585971P	P	20040706

OTHER SOURCE(S): MARPAT 138:117676

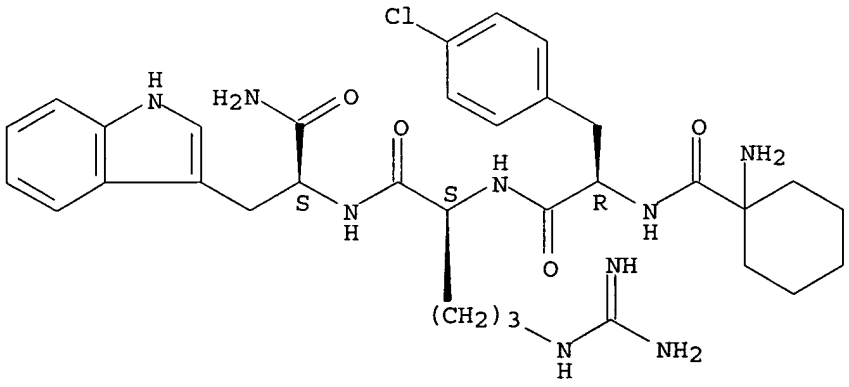
AB Linear and cyclic peptides are provided which are specific to melanocortin receptors and which exhibit agonist, antagonist, or mixed agonist-antagonist activity. The peptides of the invention may be used to treat e.g. erectile dysfunction and eating disorders.

IT **488789-57-7 488789-59-9 488789-86-2 488789-87-3**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(linear and cyclic melanocortin receptor-specific peptides, and therapeutic use)

RN 488789-57-7 HCAPLUS

CN L-Tryptophanamide, 1-aminocyclohexanecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

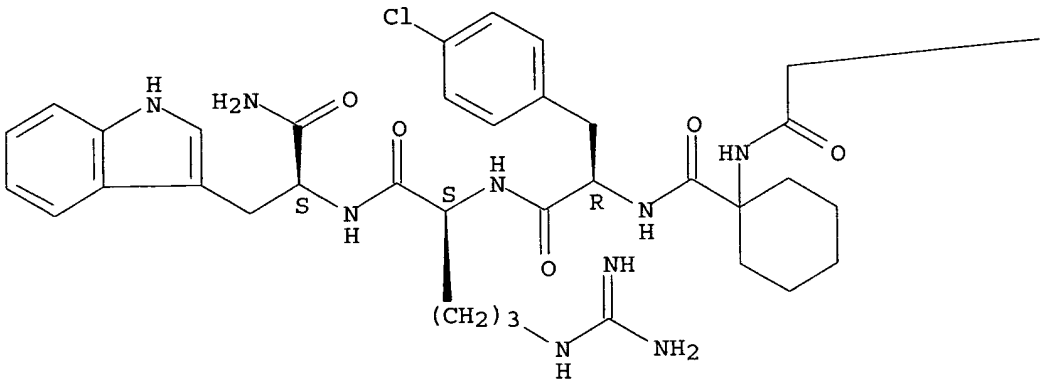


RN 488789-59-9 HCAPLUS

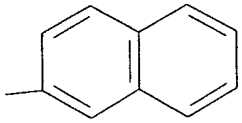
CN L-Tryptophanamide, 1-[(2-naphthalenylacetyl)amino]cyclohexanecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



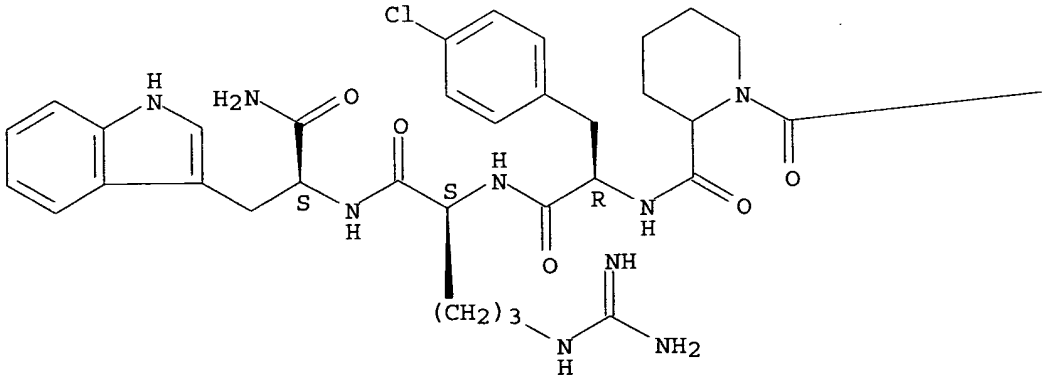
PAGE 1-B



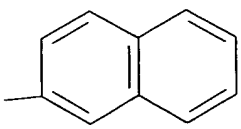
RN 488789-86-2 HCAPLUS
CN L-Tryptophanamide, 1-(2-naphthalenylcarbonyl)-2-piperidinecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

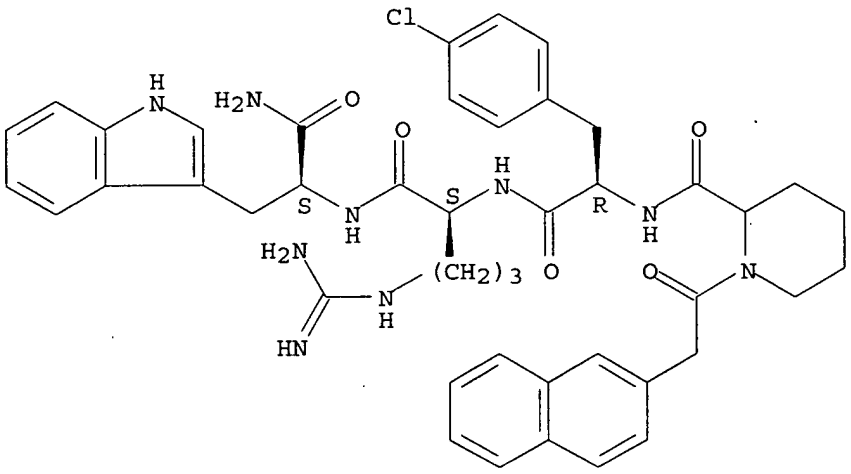


PAGE 1-B



RN 488789-87-3 HCAPLUS
CN L-Tryptophanamide, 1-(2-naphthalenylacetyl)-2-piperidinecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:847409 HCAPLUS
DOCUMENT NUMBER: 138:217330
TITLE: Cathepsin B carboxydipeptidase specificity analysis using internally quenched fluorescent peptides
AUTHOR(S): Cezari, Maria Helena S.; Puzer, Luciano; Juliano, Maria Aparecida; Carmona, Adriana K.; Juliano, Luiz
CORPORATE SOURCE: Escola Paulista de Medicina, Department of Biophysics, Universidade Federal de Sao Paulo, Sao Paulo, 04044-020, Brazil
SOURCE: Biochemical Journal (2002), 368(1), 365-369
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have examined in detail the specificity of the subsites S1, S2, S'1 and S'2 for the carboxydipeptidase activity of cathepsin B by synthesizing and assaying four series of internally quenched fluorescent peptides based on the sequence Dnp-GFRFW-OH, where Dnp (2,4-dinitrophenyl) is the quenching group of the fluorescence of the tryptophan residue. Each position, except the glycine, was substituted with 15 different naturally occurring amino acids. Based on the results we obtained, we also synthesized efficient and sensitive substrates that contained o-aminobenzoic acid and 3-Dnp-(2,3-diaminopropionic acid), or ε-amino-Dnp-Lys, as the fluorescence donor-receptor pair. The higher kinetic parameter values for the carboxydipeptidase compared with the endopeptidase activity of cathepsin B allowed an accurate anal. of its specificity. The subsite S1 accepted preferentially basic amino acids for hydrolysis; however, substrates with phenylalanine and aliphatic side-chain-containing amino acids at P1 had lower Km values. Despite the presence of Glu245 at S2, this subsite presented clear preference for aromatic amino acid residues, and the substrate with a lysine residue at P2 was hydrolyzed better than that containing an arginine residue. S'1 is essentially a hydrophobic subsite, and

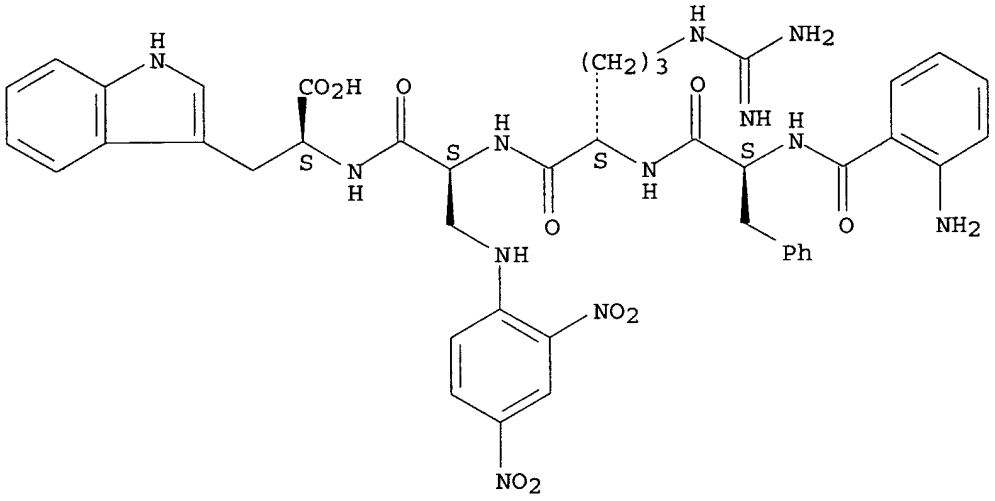
S'2 has particular preference for phenylalanine or tryptophan residues.

IT **500799-58-6 500799-60-0 500799-62-2**
500799-63-3
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(Glu245, His110 and His111 residues of occluding loop of cathepsin B play role in carboxydipeptidase activity)

RN 500799-58-6 HCAPLUS

CN L-Tryptophan, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-3-[(2,4-dinitrophenyl)amino]-L-alanyl- (9CI) (CA INDEX NAME)

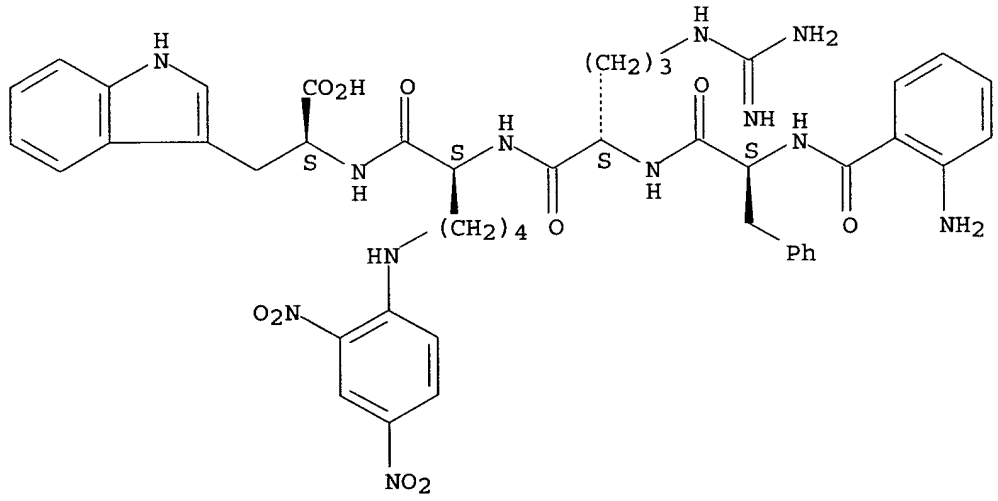
Absolute stereochemistry.



RN 500799-60-0 HCAPLUS

CN L-Tryptophan, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-N6-(2,4-dinitrophenyl)-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

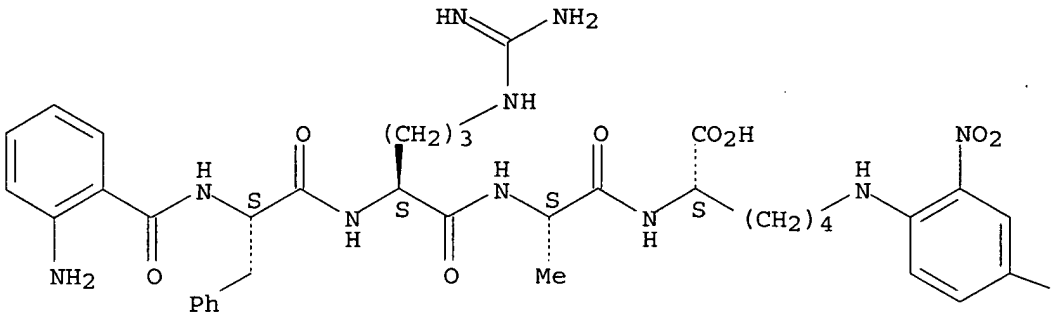


RN 500799-62-2 HCAPLUS

CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-alanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

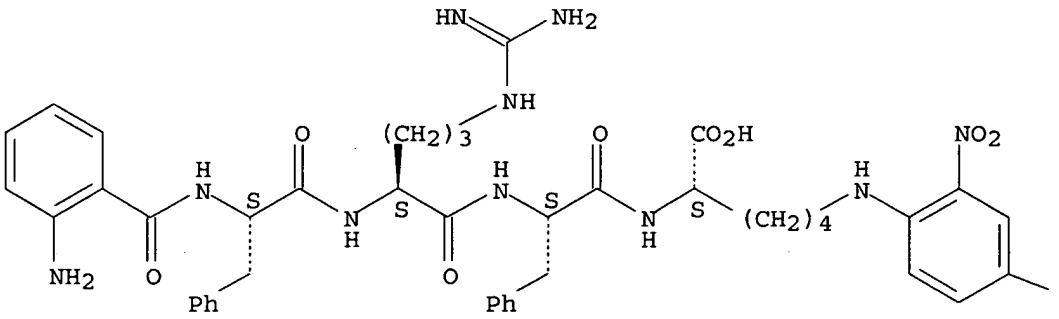


PAGE 1-B

RN 500799-63-3 HCAPLUS
CN L-Lysine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-phenylalanyl-N6-(2,4-dinitrophenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



NO_2

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:637480 HCAPLUS
DOCUMENT NUMBER: 137:190724
TITLE: Melanocortin metallopeptides for treatment of sexual dysfunction
INVENTOR(S): Sharma, Shubh D.; Shi, Yi-qun; Yang, Wei; Cai, Hui-zhi; Shadiack, Annette
PATENT ASSIGNEE(S): Palatin Technologies, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064091	A2	20020822	WO 2002-US4431	20020213
WO 2002064091	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004038897	A1	20040226	US 2003-640755	20030813
US 2005164914	A1	20050728	US 2005-36273	20050114
PRIORITY APPLN. INFO.:			US 2001-268591P	P 20010213
			US 1995-476652	A2 19950607
			US 1996-660697	A3 19960605
			US 2000-483837	A2 20000117
			WO 2002-US4431	A 20020213
			US 2003-640755	A2 20030813
			US 2004-536691P	P 20040114

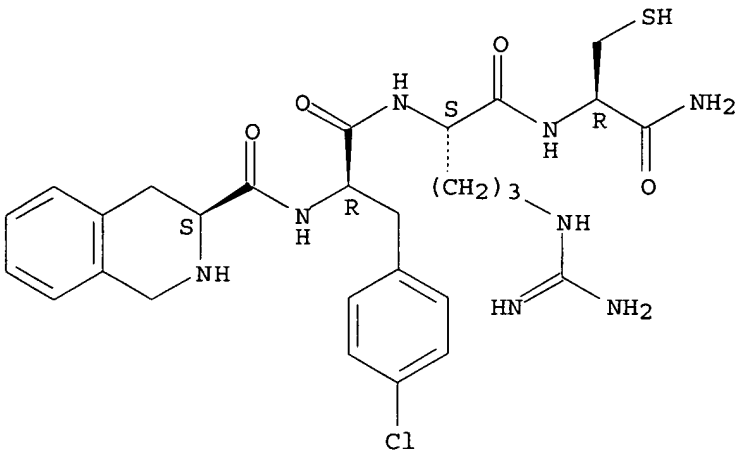
OTHER SOURCE(S): MARPAT 137:190724
AB Metallopeptides are provided for use in treatment of sexual dysfunction in mammals. The metallopeptides are agonists for at least one of

melanocortin-3 or melanocortin-4 receptors. The metallopeptides are conformationally fixed on complexation of a metal ion-binding portion thereof with a metal ion. Also provided are metallopeptides that are antagonists for at least one of melanocortin-3 or melanocortin-4 receptors.

IT **448903-52-4 448903-55-7 448903-84-2**
448904-00-5 449729-82-2 449729-83-3
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melanocortin metallopeptides for treatment of sexual dysfunction)

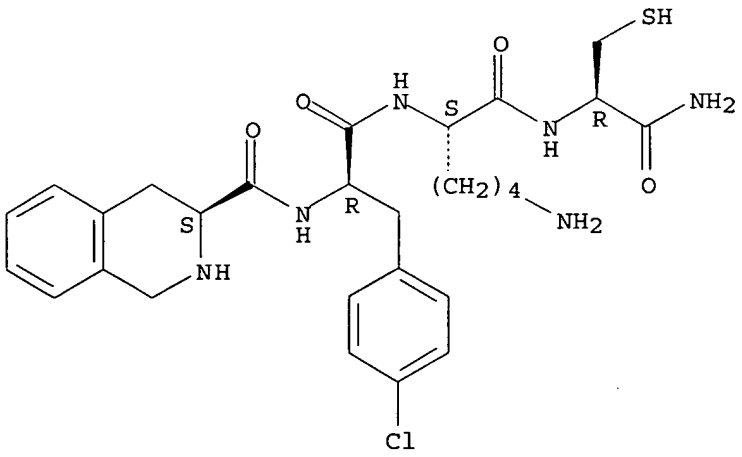
RN 448903-52-4 HCAPLUS
CN L-Cysteinamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-chloro-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 448903-55-7 HCAPLUS
CN L-Cysteinamide, (3S)-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-4-chloro-D-phenylalanyl-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

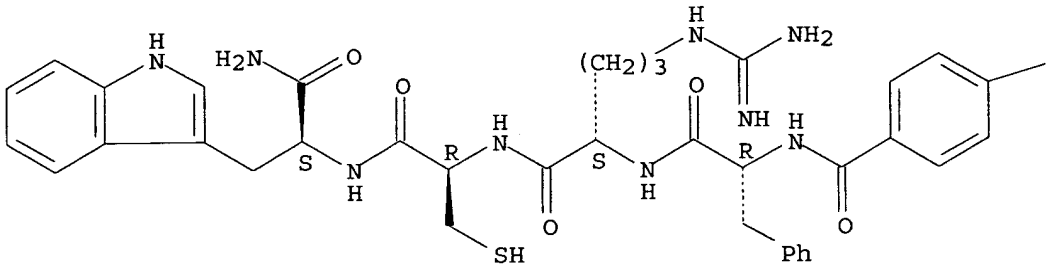


RN 448903-84-2 HCAPLUS
CN L-Tryptophanamide, N-[4-(aminomethyl)benzoyl]-D-phenylalanyl-L-arginyl-L-

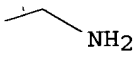
cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



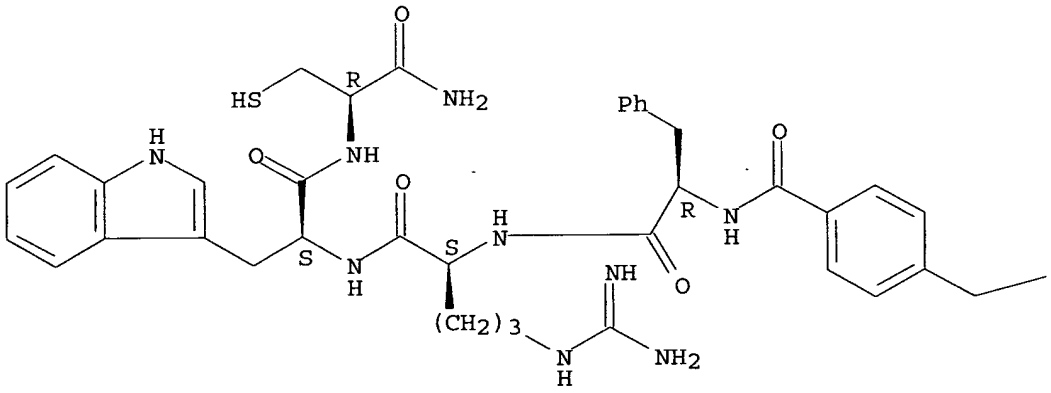
PAGE 1-B



RN 448904-00-5 HCAPLUS
CN L-Cysteinamide, N-[4-(aminomethyl)benzoyl]-D-phenylalanyl-L-arginyl-L-tryptophyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A

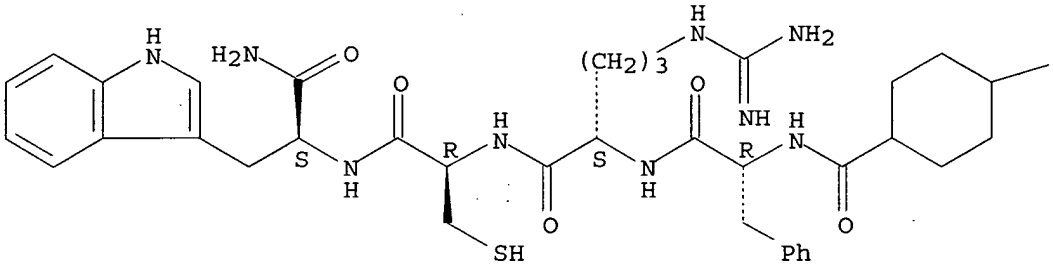


PAGE 1-B

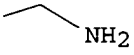
RN 449729-82-2 HCAPLUS
CN L-Tryptophanamide, N-[[4-(aminomethyl)cyclohexyl]carbonyl]-D-phenylalanyl-L-arginyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



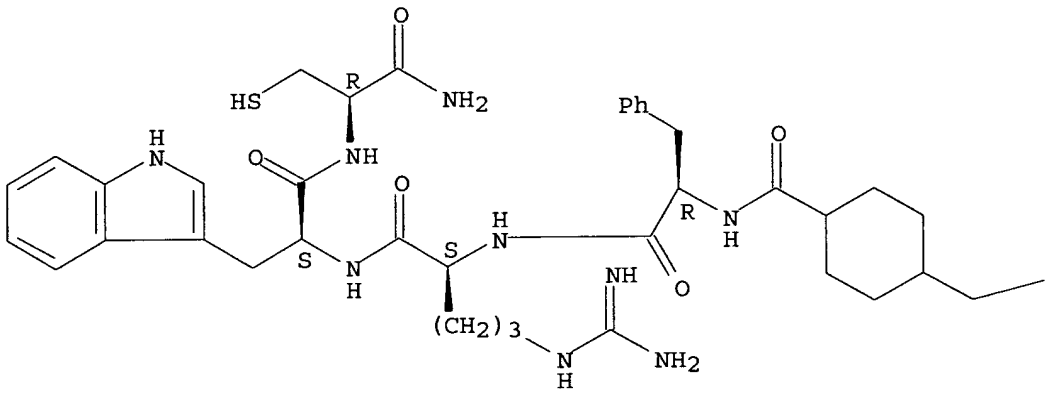
PAGE 1-B



RN 449729-83-3 HCAPLUS
CN L-Cysteinamide, N-[[4-(aminomethyl)cyclohexyl]carbonyl]-D-phenylalanyl-L-arginyl-L-tryptophyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

—NH_2

L12 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:594711 HCAPLUS
DOCUMENT NUMBER: 137:159312
TITLE: Stabilization of radiopharmaceutical compositions using hydrophilic thioethers and hydrophilic 6-hydroxy chromans
INVENTOR(S): Cyr, John E.; Pearson, Daniel A.
PATENT ASSIGNEE(S): Diatide, Inc., USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060491	A2	20020808	WO 2001-US50423	20011024
WO 2002060491	A3	20031106		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,

UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2426587	AA	20020808	CA 2001-2426587	20011024
EP 1381397	A2	20040121	EP 2001-998107	20011024
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005500982	T2	20050113	JP 2002-560682	20011024
US 2003072709	A1	20030417	US 2002-131543	20020424
US 6902718	B2	20050607		
US 2003103899	A1	20030605	US 2002-131346	20020424
US 6881396	B2	20050419		
US 2003103895	A1	20030605	US 2002-131546	20020424
US 6989138	B2	20060124		
US 2004058984	A1	20040325	US 2003-415024	20030808
US 2005207973	A1	20050922	US 2005-86966	20050322
US 2005180918	A1	20050818	US 2005-88596	20050324
PRIORITY APPLN. INFO.:			US 2000-694992	A1 20001024
			US 2000-695360	A1 20001024
			US 2000-695494	A1 20001024
			WO 2001-US50423	W 20011024
			US 2002-131346	A3 20020424
			US 2002-131543	A3 20020424

AB Radiopharmaceutical compns. which are stabilized by addition of a hydrophilic thioether, a hydrophilic 6-hydroxy-chroman derivative, or a mixture of a hydrophilic thioether and a hydrophilic 6-hydroxy-chroman derivative are described. Several examples are provided demonstrating the stabilizing effects of L-methionine, Trolox, or a combination of the two on lyophilized kit prepns. containing 99mTc-labeled depreotide, benzodiazepinedione derivative, a glycoprotein IIb/IIa receptor-binding peptide, a peptide chelator, a bisamine bisthiol chelator, or other peptides.

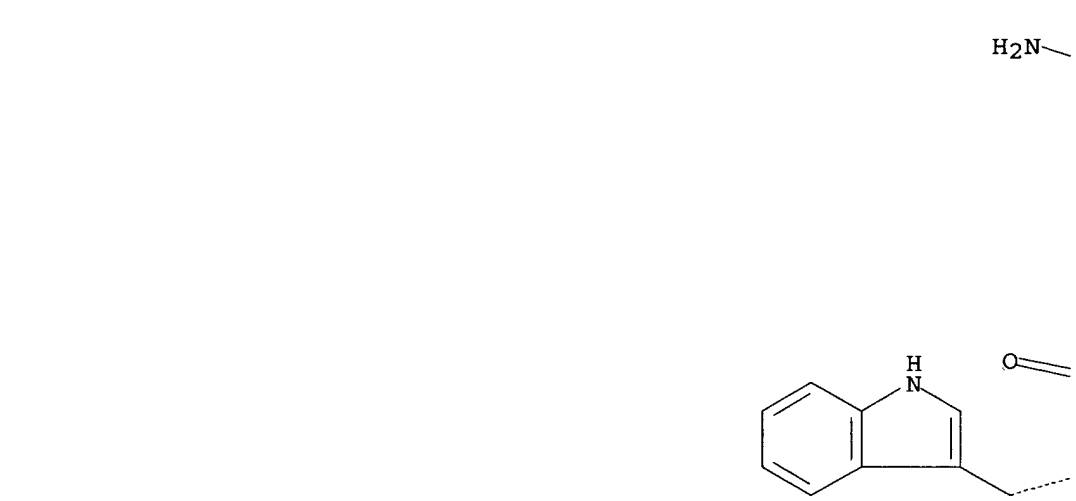
IT **161982-53-2D**, radiolabeled **445311-66-0D**, radiolabeled
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stabilization of radiopharmaceutical compns. using hydrophilic thioethers and hydrophilic hydroxychromans)

RN 161982-53-2 HCAPLUS

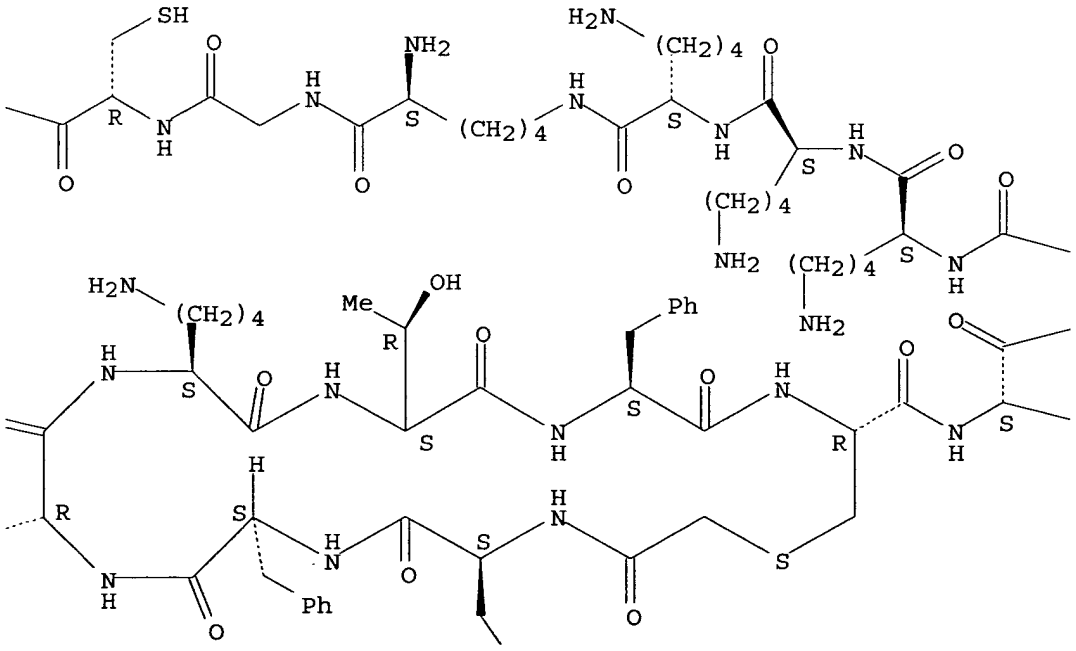
CN L-Cysteinamide, N6-[N-(mercaptoacetyl)-L-phenylalanyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-phenylalanyl-L-cysteinyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl-L-lysyl]-L-lysylglycyl-, cyclic (1→7)-thioether (9CI) (CA INDEX NAME)

Absolute stereochemistry.

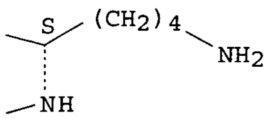
PAGE 1-A

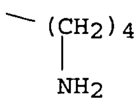


PAGE 1-B

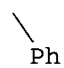


PAGE 1-C





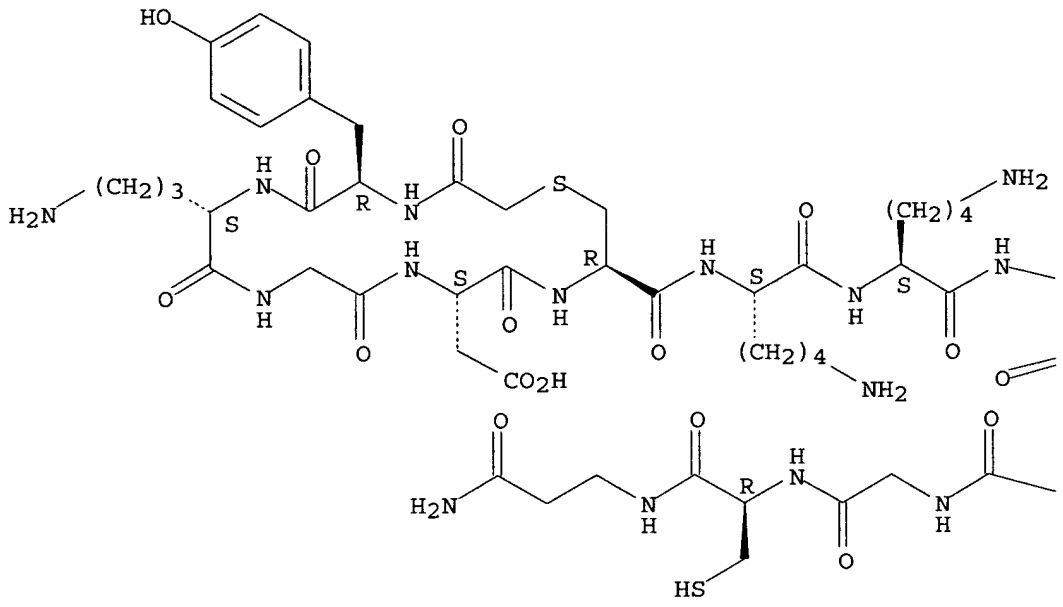
PAGE 2-B



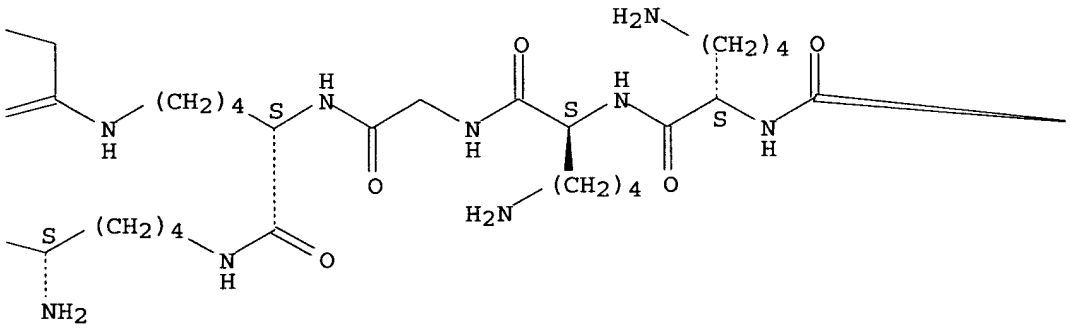
RN 445311-66-0 HCAPLUS
CN β-Alaninamide, N6-[N2,N6-bis[N-(mercaptoacetyl)-D-tyrosyl-L-ornithylglycyl-L-α-aspartyl-L-cysteinyl-L-lysyl-L-lysylglycyl]-L-lysyl]-L-lysylglycyl-L-cysteinyl-, cyclic (1→5),(1'→5')-bis(thioether) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

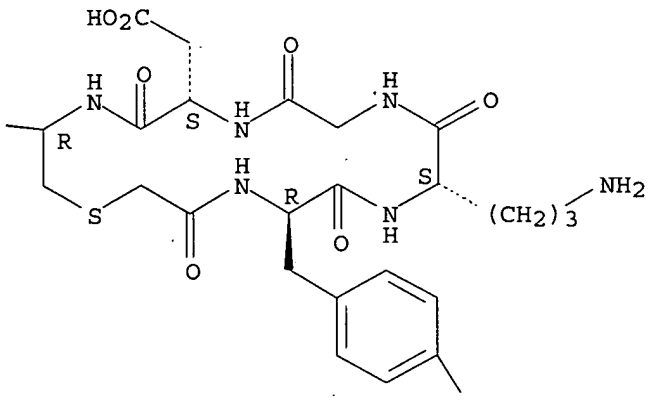
PAGE 1-A



PAGE 1-B



PAGE 1-C



PAGE 2-C

L12 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:481284 HCAPLUS
DOCUMENT NUMBER: 137:194993
TITLE: Intercalation of an Acridine-Peptide Drug in an AA/TT Base Step in the Crystal Structure of [d(CGCGAATTCGCG)]2 with Six Duplexes and Seven Mg2+ Ions in the Asymmetric Unit
AUTHOR(S): Malinina, Lucy; Soler-Lopez, Montserrat; Aymami, Joan; Subirana, Juan A.
CORPORATE SOURCE: Departament d'Enginyeria Quimica, ETSEIB, Universitat Politecnica de Catalunya, Barcelona, E-08028, Spain
SOURCE: Biochemistry (2002), 41(30), 9341-9348
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We present the crystal structure of an acridine drug derivatized at carbon 9, [Nα-(9-acridinoyl)-tetraarginine], intercalated within the dodecamer [d(CGCGAATTCGCG)]2. The presence of a lateral chain at the central carbon 9 atom differentiates this compound from most acridine drugs hitherto studied, which are usually derivatized at carbon 4. The DNA:drug interaction we observe differs from that observed in previous studies, which primarily involves shorter, mainly hexameric sequences, in two important regards: the acridine intercalates within an AA/TT base step, rather than

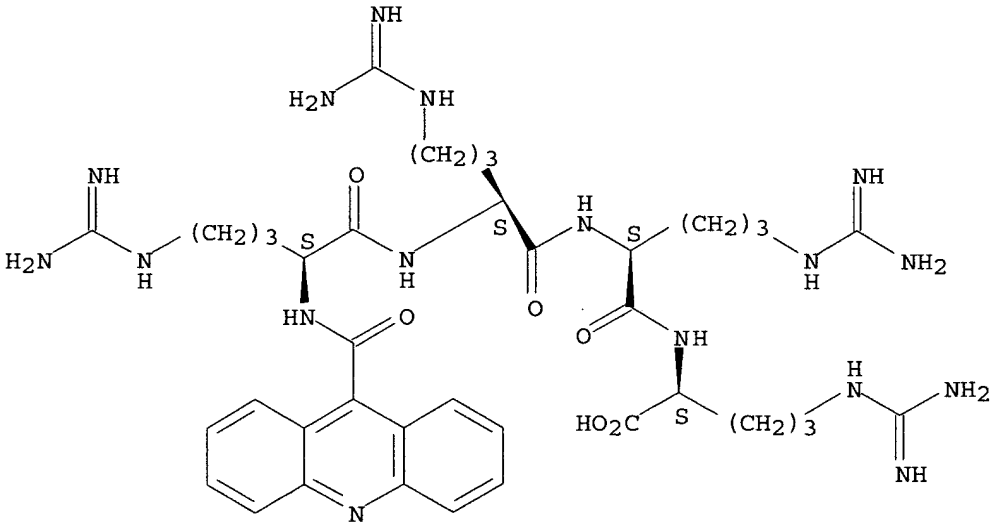
within a CG/CG base step; and the binding site is located at the center of the sequence, rather than at one end of the duplex. In addition, we observe a novel crystal packing arrangement, with six dodecamer duplexes and seven hydrated magnesium ions in the asym. unit of a large (66.5 + 68.4 + 77.4 Å3) unit cell in space group P212121. The duplexes are organized in layers parallel to the ab plane, with consecutive layers crossing each other at right angles.

IT **452081-70-8D**, intercalating complexes with DNA
RL: PRP (Properties)
(intercalation of acridine-peptide drug in AA/TT base step in crystal structure of [d(CGCGAATTCGCG)]2 with six duplexes and seven Mg2+ ions in asym. unit)

RN 452081-70-8 HCAPLUS

CN L-Arginine, N2-(9-acridinylcarbonyl)-L-arginyl-L-arginyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:394477 HCAPLUS

DOCUMENT NUMBER: 137:103998

TITLE: Structure-Activity Relationships of the Melanocortin Tetrapeptide Ac-His-DPhe-Arg-Trp-NH2 at the Mouse Melanocortin Receptors. 1. Modifications at the His Position

AUTHOR(S): Holder, Jerry Ryan; Bauzo, Rayna M.; Xiang, Zhimin; Haskell-Luevano, Carrie

CORPORATE SOURCE: Department of Medicinal Chemistry, University of Florida, Gainesville, FL, 32610, USA

SOURCE: Journal of Medicinal Chemistry (2002), 45(13), 2801-2810
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

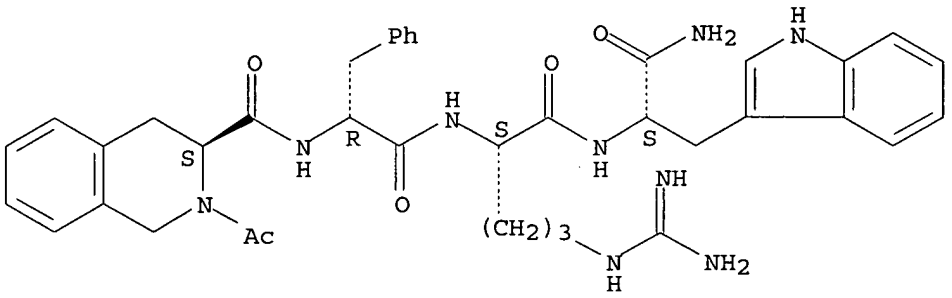
AB The melanocortin pathway is an important participant in obesity and energy

homeostasis. The centrally located melanocortin-3 and melanocortin-4 receptors (MC3R, MC4R) are involved in the metabolic and food intake aspects of energy homeostasis and are stimulated by melanocortin agonists such as α-melanocyte stimulation hormone (α-MSH). The melanocortin agonists contain the putative message sequence "His-Phe-Arg-Trp", and it has been well documented that inversion of chirality of the Phe to DPhe results in a dramatic increase in melanocortin receptor potency. Herein, the authors report a tetrapeptide library based on the template Ac-His-DPhe-Arg-Trp-NH2, consisting of 17 members that have been modified at the His6 position (α-MSH numbering) and pharmacol. characterized for agonist activity at the mouse melanocortin receptors MC1R, MC3R, MC4R, and MC5R. These studies provide further exptl. evidence that the His6 position can determine MC4R vs. MC3R agonist selectivity and that chemical nonreactive side chains may be substituted for the imidazole ring (generally needs to be side chain protected in synthetic schemes) in the design of MC4R-selective, small-mol., non-peptide agonists. Specifically, the tetrapeptide containing the amino-2-naphthylcarboxylic acid (Anc) amino acid at the His position resulted in a potent agonist at the mMC4R (EC50 = 21 nM), was a weak mMC3R micromolar antagonist (pA2 = 5.6, Ki = 2.5 μM), and possessed >4700-fold agonist selectivity for the MC4R vs. the MC3R. Substitution of the His6 amino acid in the tetrapeptide template by the Phe, Anc, 3-(2-thienyl)alanine (2Thi), and 3-(4-pyridinyl)alanine (4-Pal) resulted in equipotency or only up to a 7-fold decrease in potency, compared to the His6-containing tetrapeptide at the mMC4R, demonstrating that these amino acid side chains may be substituted for the imidazole in the design of MC4R-selective non-peptide mols.

IT **443789-84-2P 443789-86-4P 443789-97-7P**
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(structure-activity relationships of melanocortin tetrapeptide analogs at mouse melanocortin receptors)

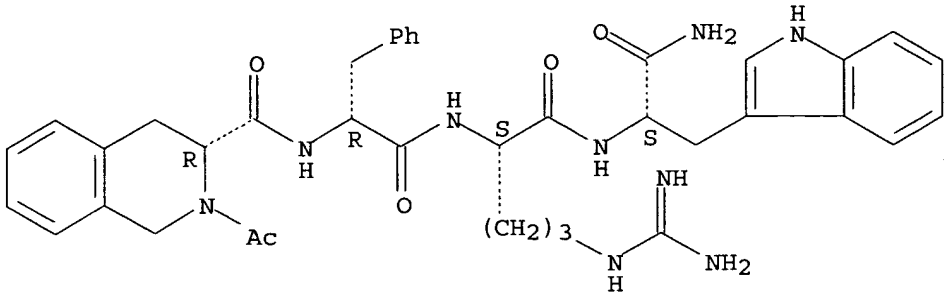
RN 443789-84-2 HCAPLUS
CN L-Tryptophanamide, (3S)-2-acetyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



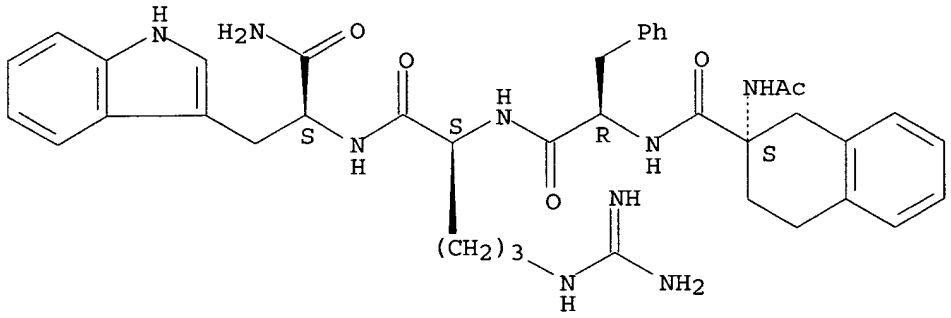
RN 443789-86-4 HCAPLUS
CN L-Tryptophanamide, (3R)-2-acetyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 443789-97-7 HCAPLUS
CN L-Tryptophanamide, (2S)-2-(acetylamino)-1,2,3,4-tetrahydro-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:747815 HCAPLUS
DOCUMENT NUMBER: 135:304143
TITLE: Preparation of selective linear peptides with melanocortin-4 receptor (MC4-R) agonist activity
INVENTOR(S): Chen, Li; Cheung, Adrian Wai-hing; Chu, Xin-jie; Danho, Waleed; Swistok, Joseph; Yagaloff, Keith Alan
PATENT ASSIGNEE(S): F. Hoffmann-La Roche Ag, Switz.
SOURCE: PCT Int. Appl., 265 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074844	A2	20011011	WO 2001-EP3529	20010327
WO 2001074844	A3	20020613		

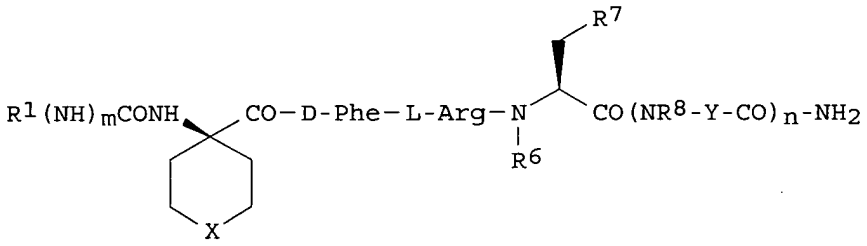
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG,

KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2001056179	A1	20011227	US 2001-811964		20010319
US 6600015	B2	20030729			
CA 2402416	AA	20011011	CA 2001-2402416		20010327
EP 1272516	A2	20030108	EP 2001-923703		20010327
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2003529607	T2	20031007	JP 2001-572533		20010327
US 2003229200	A1	20031211	US 2003-435466		20030509
US 2005239711	A1	20051027	US 2005-159007		20050622
PRIORITY APPLN. INFO.:			US 2000-194450P	P	20000404
			US 2001-811964	A1	20010319
			WO 2001-EP3529	W	20010327
			US 2003-435466	B1	20030509

OTHER SOURCE(S): MARPAT 135:304143

GI



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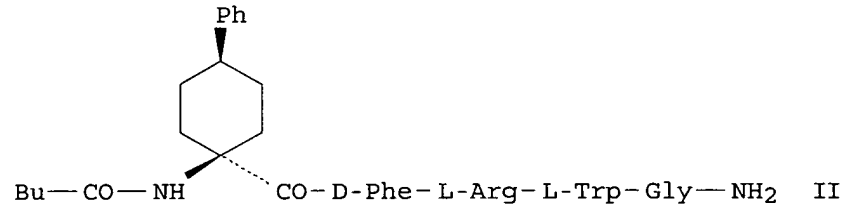


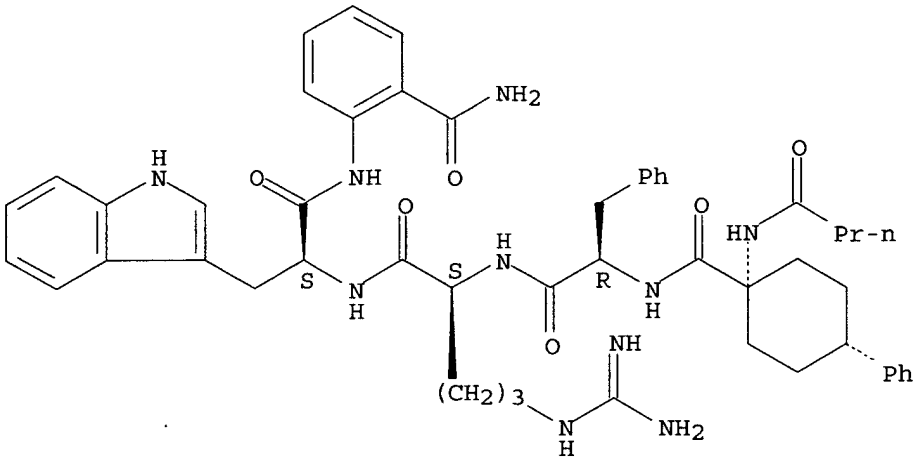
II

AB Peptides I [m, n = 0, 1; R1 = (un)substituted alkyl, phenylalkyl, carboxyalkyl or phenyl; X = phenylmethylene or alkoxyphenylmethylene, cyclohexyl-, cycloheptyl- or alkylmethylene, or (un)substituted phenylimino; R6, R8 = H, Me; R7 = 3-indolyl, 1- or 2-naphthyl; Y = CH2, CH2CH2, CHMe, CH2C6H4-m or p- or o-C6H4 (with provisos)] or an analog in which X-CH2 is (un)substituted benzo were prepared as MC4-R agonists. Thus, pentapeptide II [pentaApc-D-Phe-Arg-Trp-Gly-NH2] was prepared by the solid-phase method using a Fmoc-Linker-BHA resin.

IT **365552-10-9P 365552-13-2P 365552-15-4P**
365552-16-5P 365552-17-6P 365552-20-1P
365552-23-4P 365552-25-6P 365552-35-8P
365552-38-1P 365552-40-5P 365552-97-2P
365552-99-4P 365553-01-1P 365553-09-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of selective linear peptides with melanocortin-4 receptor (MC4-R) agonist activity)

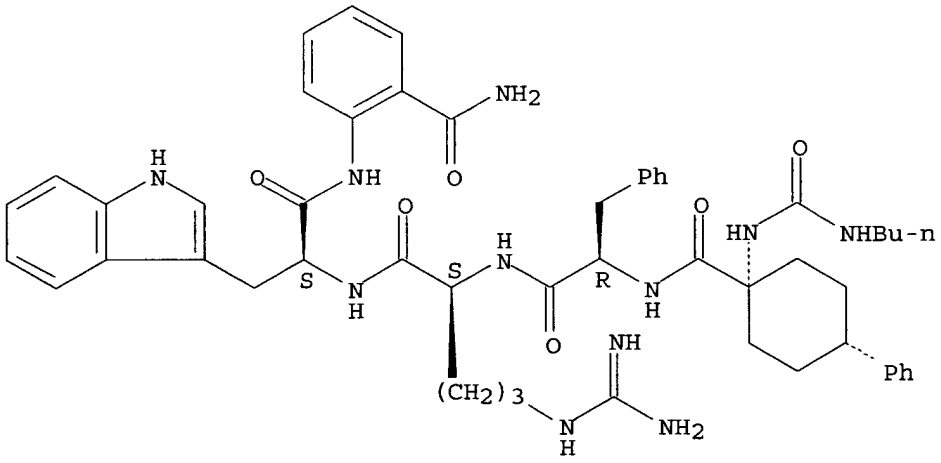
RN 365552-10-9 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



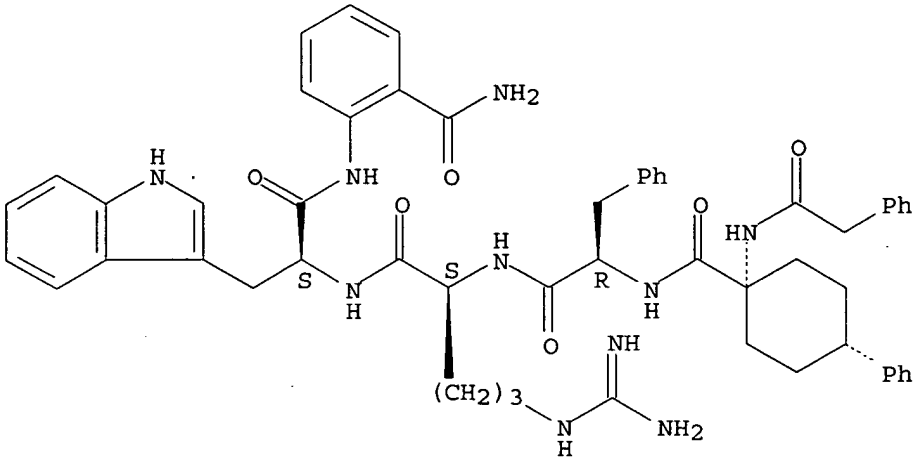
RN 365552-13-2 HCAPLUS
CN L-Tryptophanamide, cis-1-[[(butylamino)carbonyl]amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



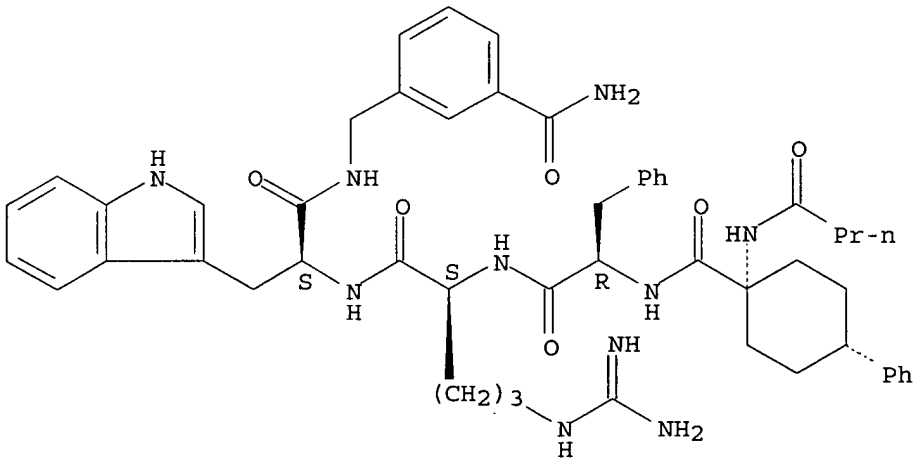
RN 365552-15-4 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



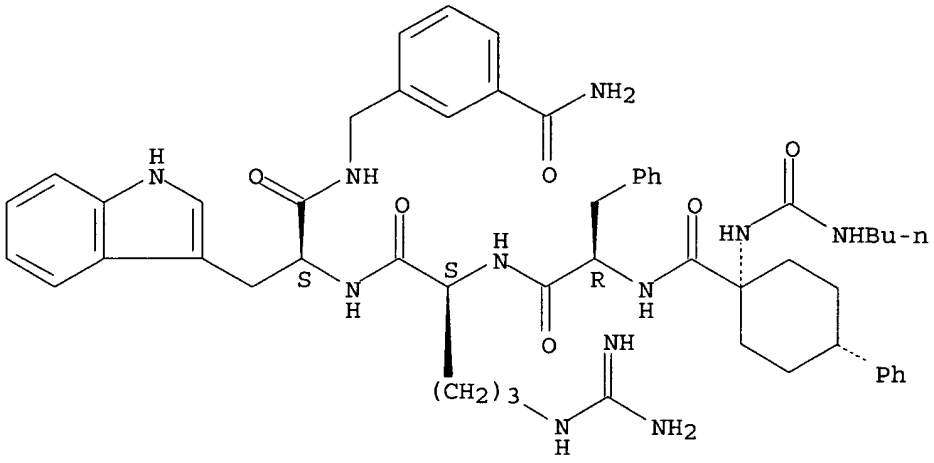
RN 365552-16-5 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



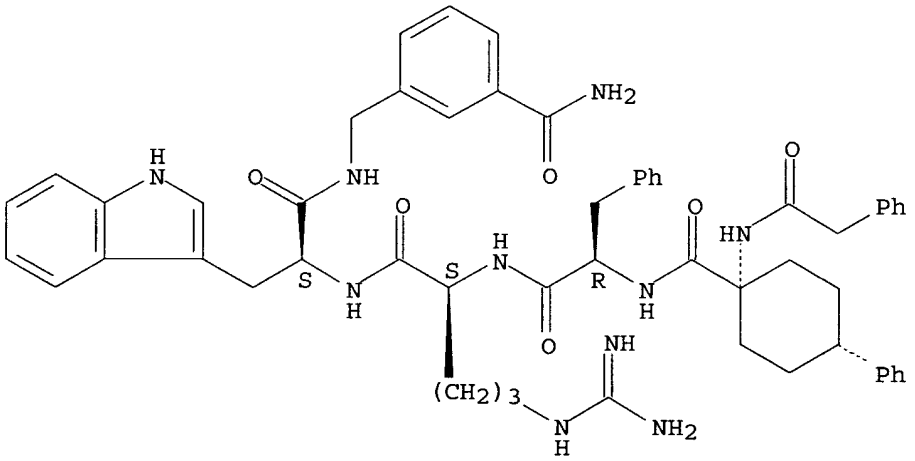
RN 365552-17-6 HCAPLUS
CN L-Tryptophanamide, cis-1-[[(butylamino)carbonyl]amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



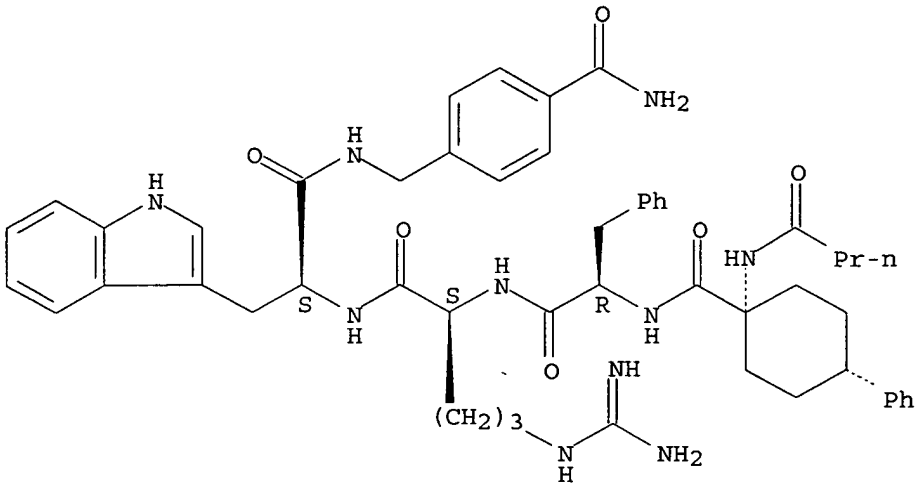
RN 365552-20-1 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



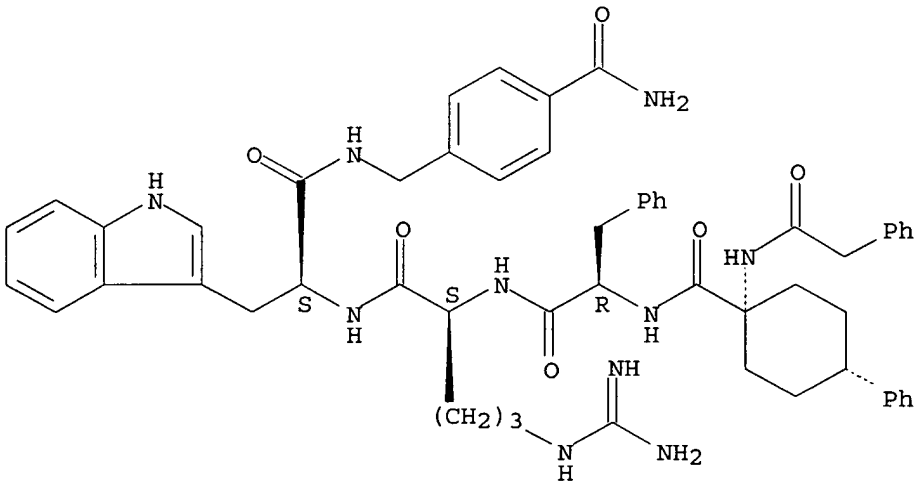
RN 365552-23-4 HCAPLUS
CN L-Tryptophanamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



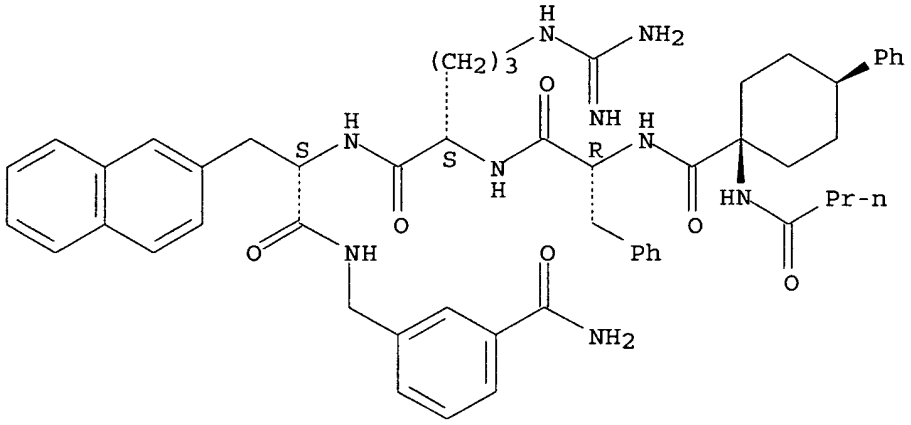
RN 365552-25-6 HCAPLUS
CN L-Tryptophanamide, cis-4-phenyl-1-[(phenylacetyl)amino]cyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



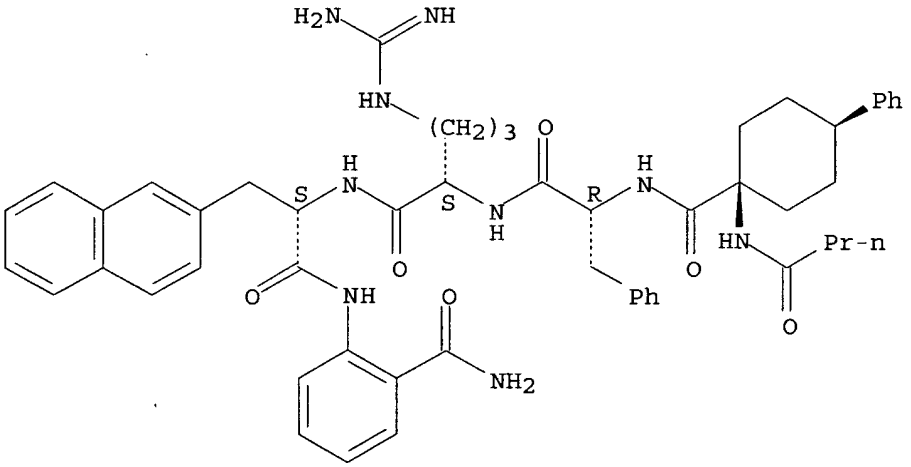
RN 365552-35-8 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[3-(aminocarbonyl)phenyl]methyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



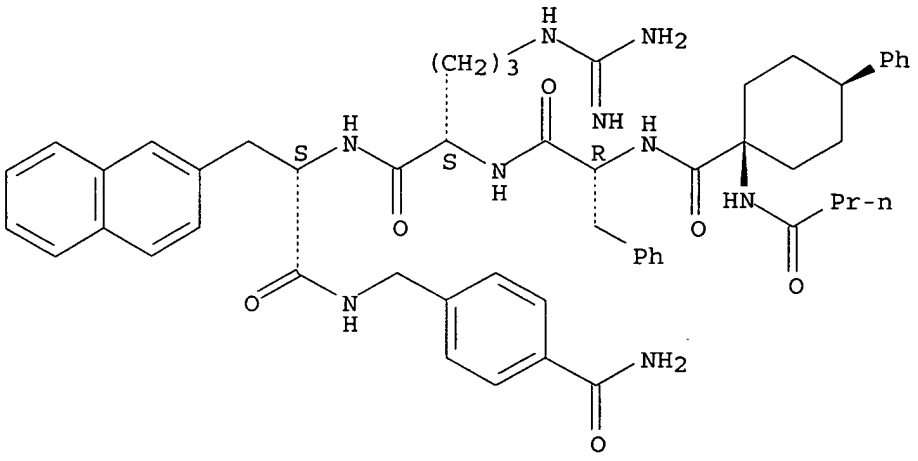
RN 365552-38-1 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



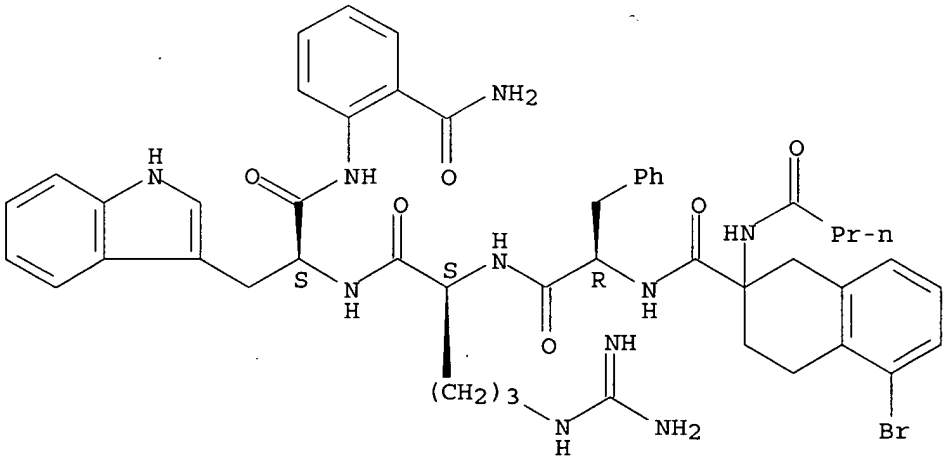
RN 365552-40-5 HCAPLUS
CN L-Alaninamide, cis-1-[(1-oxobutyl)amino]-4-phenylcyclohexanecarbonyl-D-phenylalanyl-L-arginyl-N-[[4-(aminocarbonyl)phenyl]methyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



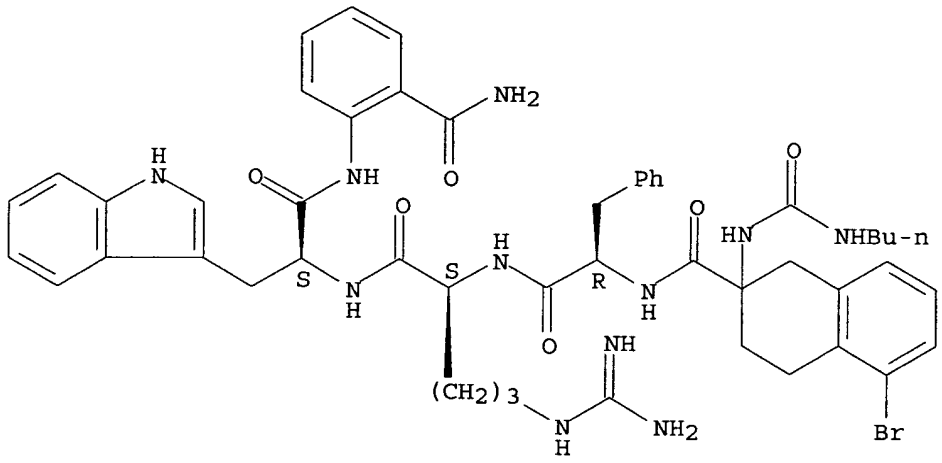
RN 365552-97-2 HCAPLUS
CN L-Tryptophanamide, 5-bromo-1,2,3,4-tetrahydro-2-[(1-oxobutyl)amino]-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



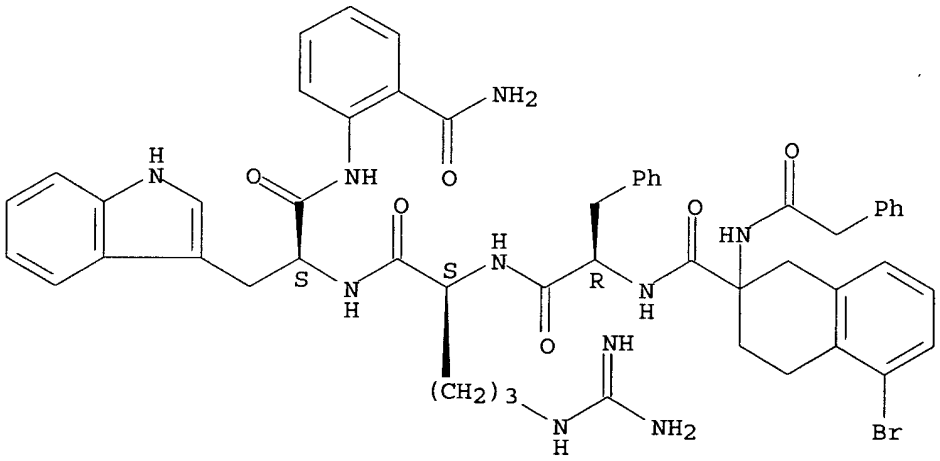
RN 365552-99-4 HCAPLUS
CN L-Tryptophanamide, 5-bromo-2-[[(butylamino)carbonyl]amino]-1,2,3,4-tetrahydro-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



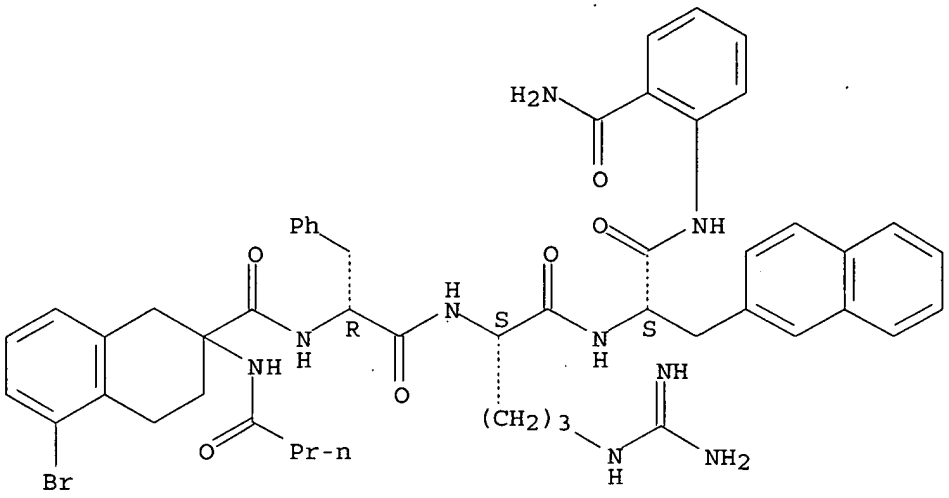
RN 365553-01-1 HCAPLUS
CN L-Tryptophanamide, 5-bromo-1,2,3,4-tetrahydro-2-[(phenylacetyl)amino]-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 365553-09-9 HCAPLUS
CN L-Alaninamide, 5-bromo-1,2,3,4-tetrahydro-2-[(1-oxobutyl)amino]-2-naphthalenecarbonyl-D-phenylalanyl-L-arginyl-N-[2-(aminocarbonyl)phenyl]-3-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:677356 HCAPLUS
DOCUMENT NUMBER: 135:195790
TITLE: Preparation of peptides which inhibit human tissue kallikrein and the liberation of kinins
INVENTOR(S): De Nucci, Gilberto; Juliano Neto, Luiz; Giuseppe, Caliendo; Vincenzo, Santagada
PATENT ASSIGNEE(S): Laboratorios Biosintetica Ltda, Brazil; Universidade Federal de Sao Paulo -UNIFESP
SOURCE: Braz. Pedido PI, 11 pp.
CODEN: BPXXDX
DOCUMENT TYPE: Patent
LANGUAGE: Portuguese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BR 9900694	A	20001017	BR 1999-694	19990308

PRIORITY APPLN. INFO.: BR 1999-694 19990308

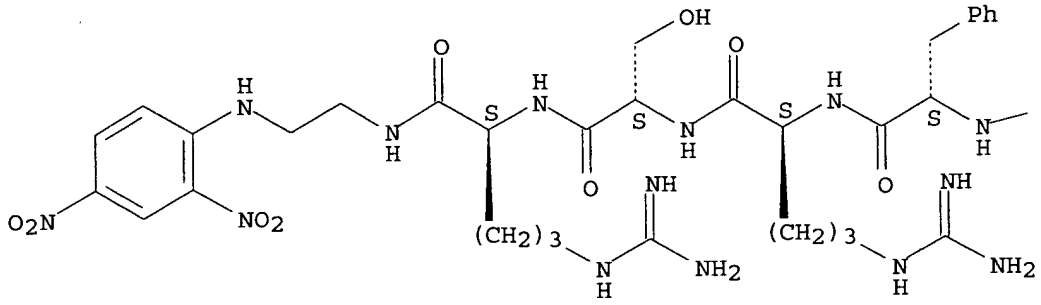
AB Analogs of o-H2NC6H4CO-Phe-Arg-Arg-Pro-NHCH2CH2NHC6H3(NO2)2-2,4 and peptides PhCH2CO-X-Ser-Arg-NH2 (X represents certain non-natural amino acids) were prepared as inhibitors of human tissue kallikrein and the liberation of kinins for use as inflammation inhibitors and analgesics. Thirty claimed compds. were prepared by the solid-phase method.

IT **133839-14-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of peptides which inhibit human tissue kallikrein and the liberation of kinins)

RN 133839-14-2 HCAPLUS
CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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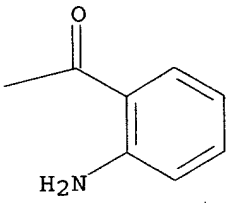


L12 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:519335 HCAPLUS
DOCUMENT NUMBER: 135:111977
TITLE: Diagnostic/therapeutic agents having phospholipid-based microbubbles coupled to one or more vectors
INVENTOR(S): Klaveness, Jo; Rongved, Pal; Hogset, Anders; Tolleshaug, Helge; Naevestad, Anne; Hellebust, Halldis; Hoff, Lars; Cuthbertson, Alan; Lovhaug, Dagfinn; Solbakken, Magne
PATENT ASSIGNEE(S): Nycomed Imaging As, Norway
SOURCE: U.S., 89 pp., Cont.-in-part of U.S. Ser. No. 958,993.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6261537	B1	20010717	US 1997-960054	19971029
CN 1234742	A	19991110	CN 1997-199047	19971028
US 6331289	B1	20011218	US 1997-959206	19971028
EP 1442751	A1	20040804	EP 2004-7226	19980424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
ES 2224379	T3	20050301	ES 1998-917461	19980424
KR 2000052829	A	20000825	KR 1999-703658	19990427
US 2002102215	A1	20020801	US 2001-765614	20010122
US 2002102217	A1	20020801	US 2001-925715	20010810
US 6680047	B2	20040120		

CN 1440816	A	20030910	CN 2002-160420		20021230
US 2004141922	A1	20040722	US 2003-722075		20031126
US 2005002865	A1	20050106	US 2003-734730		20031215
PRIORITY APPLN. INFO.:			GB 1996-22366	A	19961028
			GB 1996-22367	A	19961028
			GB 1996-22368	A	19961028
			GB 1997-699	A	19970115
			GB 1997-8265	A	19970424
			GB 1997-11842	A	19970606
			GB 1997-11846	A	19970606
			US 1997-49264P	P	19970606
			US 1997-49265P	P	19970606
			US 1997-49268P	P	19970606
			US 1997-958993	A2	19971028
			GB 1996-22369	A	19961028
			GB 1997-2195	A	19970204
			GB 1997-11837	A	19970606
			GB 1997-11839	A	19970606
			US 1997-49263P	P	19970607
			US 1997-49266P	P	19970607
			US 1997-959206	A	19971028
			US 1997-960054	A1	19971029
			EP 1998-917461	A3	19980424
			US 2001-765614	B1	20010122
			US 2001-925715	A1	20010810

AB Targetable diagnostic and/or therapeutically active agents, e.g. ultrasound contrast agents, having reporters comprise gas-filled microbubbles stabilized by monolayers of film-forming surfactants, the reporter being coupled or linked to at least one vector. The gas is air, nitrogen, oxygen, carbon dioxide, hydrogen, an inert gas, a sulfur fluoride, selenium hexafluoride, a low mol. weight hydrocarbon, a ketone, an ester, a halogenated low mol. weight hydrocarbon or their mixts. The film-forming surfactant material is one or more phospholipids selected from the group consisting of phosphatidylserines, phosphatidylglycerols, phosphatidylinositols, phosphatidic acids and cardiolipins. A therapeutic agent is an antineoplastic agent, blood product, biol. response modifier, antifungal agent, hormone or hormone analog, vitamin, enzyme, antiallergic agent, tissue factor inhibitor, platelet inhibitor, coagulation protein target inhibitor, fibrin formation inhibitor, fibrinolysis promoter, antiangiogenic, circulatory drug, metabolic potentiator, antitubercular, antiviral, vasodilator, antibiotic, anti-inflammatory, antiprotozoal, antirheumatic, narcotic, opiate, cardiac glycoside, neuromuscular blocker, sedative, local anesthetic, general anesthetic or genetic material. For example, an endothelial cell adhesion of phosphatidylserine-encapsulated perfluorobutane microbubbles coated with polylysine was higher than adhesion of uncoated microbubbles. Also, a thrombus was detected by ultrasound in patients with suspected venous thrombosis using i.v. phosphatidylserine-encapsulated microbubbles. The microbubbles contained inactivated human thrombin-succinyl-PEG 3400-distearoylphosphatidylethanol amine incorporated into the encapsulating membrane.

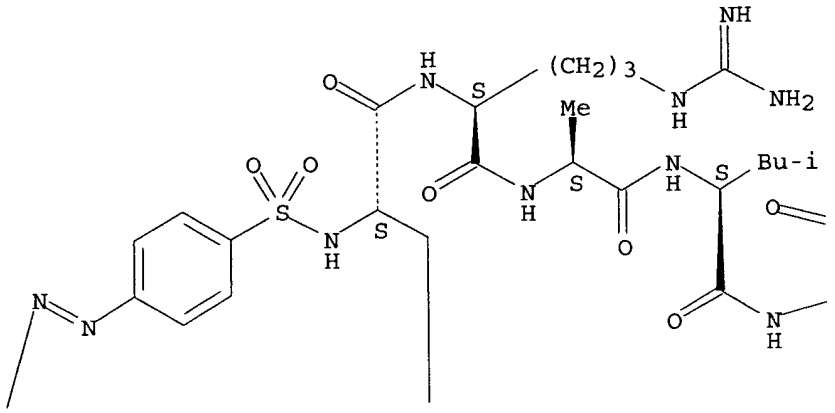
IT **207302-67-8P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diagnostic/therapeutic agents having phospholipid-based gas-filled microbubbles coupled to one or more vectors)

RN 207302-67-8 HCAPLUS

CN L-Cysteine, N-[[4-[[4-(dimethylamino)phenyl]azo]phenyl]sulfonyl]-L-tyrosyl-L-arginyl-L-alanyl-L-leucyl-L-valyl-L-α-aspartyl-L-threonyl-L-leucyl-L-lysyl-N6-(L-arginylglycyl-L-α-aspartyl-L-seryl)-L-lysylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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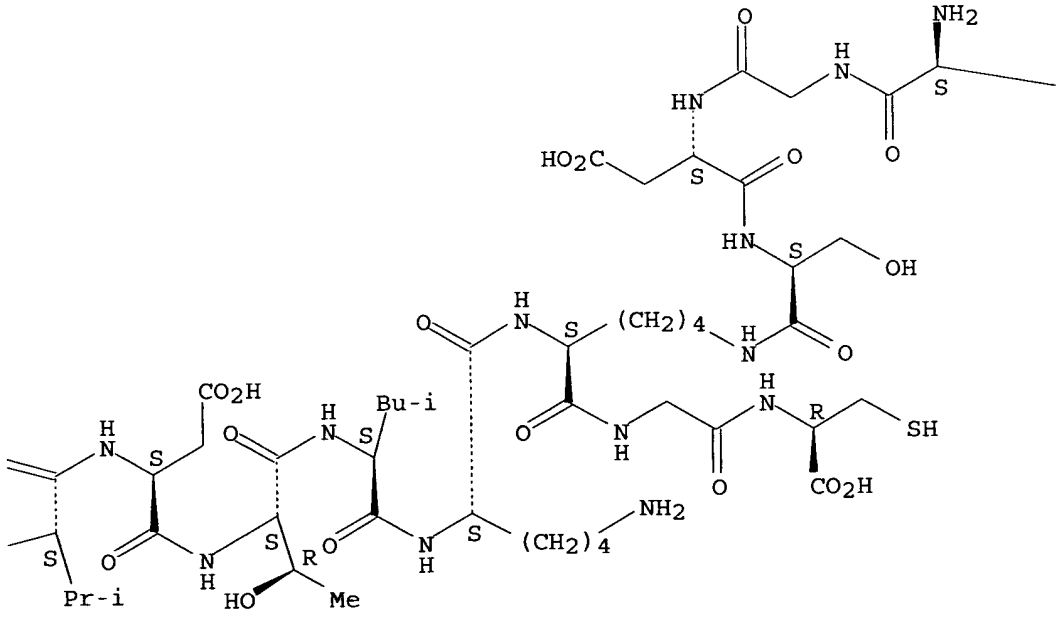
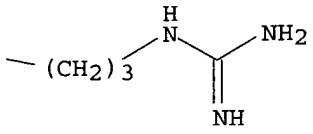


PAGE 1-C



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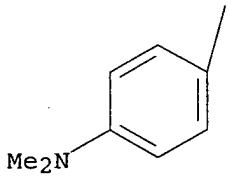
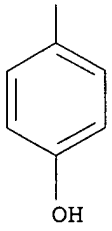




REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:429240 HCAPLUS
DOCUMENT NUMBER: 135:223214
TITLE: Purification and characterization of active recombinant rat kallikrein rK9
AUTHOR(S): Zani, M.-L.; Brillard-Bourdet, M.; Lazure, C.; Juliano, L.; Courty, Y.; Gauthier, F.; Moreau, T.
CORPORATE SOURCE: Laboratory of Enzymology and Protein Chemistry, INSERM EMI-U 00-10, University Francois Rabelais, Tours, 37032, Fr.
SOURCE: Biochimica et Biophysica Acta, Protein Structure and Molecular Enzymology (2001), 1547(2), 387-396
CODEN: BBAEDZ; ISSN: 0167-4838
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The rat tissue kallikrein rK9 is most abundant in the submandibular gland and the prostate. It has been successfully expressed in the Pichia pastoris yeast expression system. A full-length cDNA coding for the mature rK9 was fused in frame with yeast α-factor cDNA. The fusion protein was secreted into the medium with high yield without being processed by the yeast KEX2 signal peptidase. Mature rK9 was efficiently released from the fusion protein by trypsin and was purified to homogeneity by one-step affinity chromatog. using soya bean trypsin inhibitor (SBTI) as affinity ligand. The identity of the recombinant enzyme was checked by N-terminal amino acid sequencing, Western blot anal. and kinetic studies. The dual trypsin- and chymotrypsin-like enzymic specificity of rK9 was assessed by determining specificity consts. (kcat/Km) for the hydrolysis of fluorogenic substrates, the peptide sequences of which were derived from proparathyroid hormone (pro-PTH) and from semenogelin-I. Our results confirmed the presence of an extended binding site in the rK9 active site. We also identified a far more sensitive substrate of this

enzyme than those previously described, Abz-VKKRSARQ-EDDnp, which was hydrolyzed with a catalytic efficiency kcat/Km of 420000 M-1s-1. Finally, we showed that four of the five major proteins contained in secretions of rat seminal vesicles were rapidly degraded by recombinant rK9.

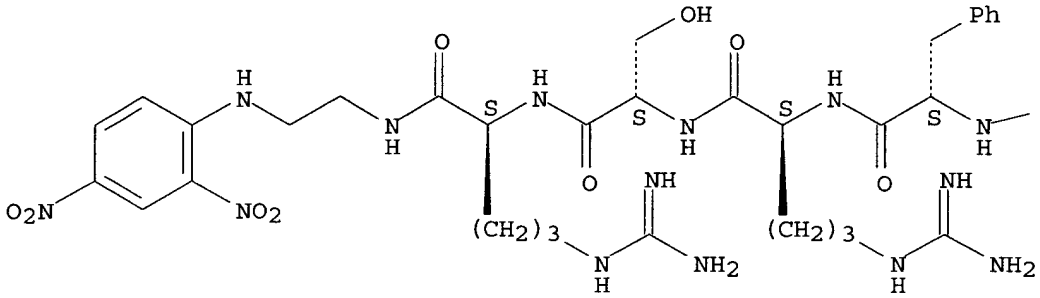
IT **133839-14-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(expression in Pichia pastoris, purification and characterization of active recombinant rat kallikrein rK9)

RN 133839-14-2 HCAPLUS

CN L-Argininamide, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-L-seryl-N-[2-[(2,4-dinitrophenyl)amino]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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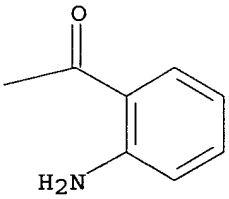


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:84505 HCAPLUS

DOCUMENT NUMBER: 134:291943

TITLE: Cathepsins X and B can be differentiated through their respective mono- and dipeptidyl carboxypeptidase activities

AUTHOR(S): Therrien, Christian; Lachance, Paule; Sulea, Traian; Purisima, Enrico O.; Qi, Hongtao; Ziomek, Edmund; Alvarez-Hernandez, Alejandro; Roush, William R.; Menard, Robert

CORPORATE SOURCE: Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P 2R2, Can.

SOURCE: Biochemistry (2001), 40(9), 2702-2711
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English

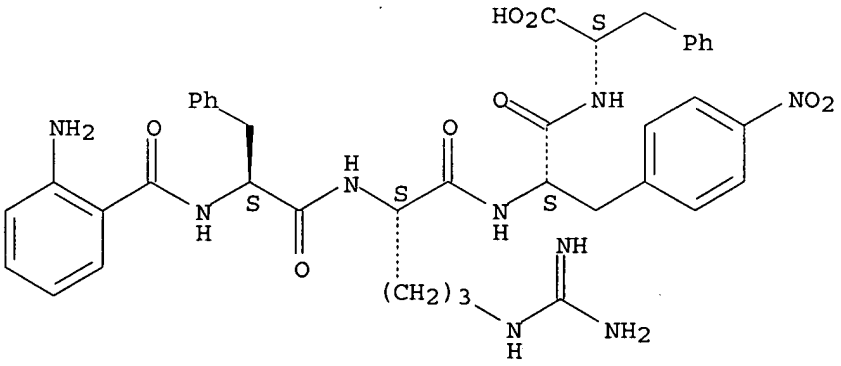
AB Several new cysteine proteases of the papain family have been discovered in the past few years. To help in the assignment of physiol. roles and in the design of specific inhibitors, a clear picture of the specificities of these enzymes is needed. One of these novel enzymes, cathepsin X, displays a unique specificity, cleaving single amino acid residues at the C-terminus of substrates very efficiently. In this study, the carboxypeptidase activities and substrate specificity of cathepsins X and B have been investigated in detail and compared. Using quenched fluorogenic substrates and HPLC measurements, it was shown that cathepsin X preferentially cleaves substrates through a monopeptidyl carboxypeptidase pathway, while cathepsin B displays a preference for the dipeptidyl pathway. The preference for one or the other pathway is about the same for both enzymes, i.e., approx. 2 orders of magnitude, a result supported by mol. modeling of enzyme-substrate complexes. Cleavage of a C-terminal dipeptide of a substrate by cathepsin X can become more important under conditions that preclude efficient monopeptidyl carboxypeptidase activity, e.g., nonoptimal interactions in subsites S2-S1. These results confirm that cathepsin X is designed to function as a monopeptidyl carboxypeptidase. Contrary to a recent report [Klemencic, I., et al. (2000) Eur. J. Biochem. 267, 5404-5412], it is shown that cathepsins X and B do not share similar activity profiles, and that reagents are available to clearly distinguish the two enzymes. In particular, CA074 was found to inactivate cathepsin B at least 34000-fold more efficiently than cathepsin X. The insights obtained from this and previous studies have been used to produce an inhibitor designed to exploit the unique structural features responsible for the carboxypeptidase activity of cathepsin X. Although of moderate potency, this E-64 derivative is the first reported example of a cathepsin X-specific inhibitor.

IT **334772-24-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(cathepsins X and B can be differentiated through resp. mono- and dipeptidyl carboxypeptidase activities)

RN 334772-24-6 HCAPLUS

CN L-Phenylalanine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-4-nitro-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

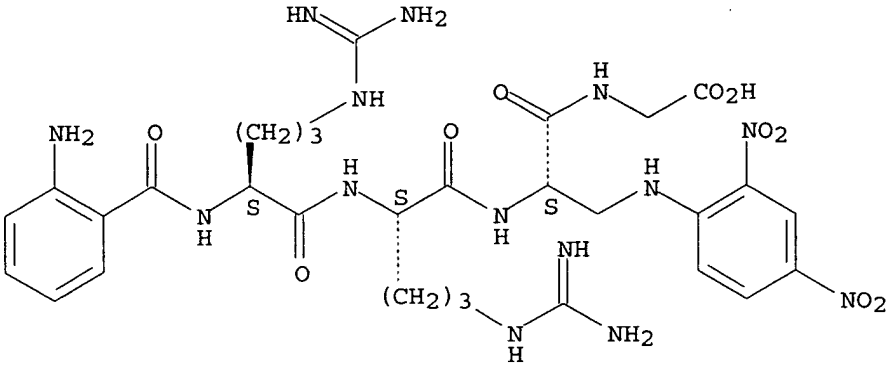
L12 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:36316 HCAPLUS
DOCUMENT NUMBER: 134:233492
TITLE: Substrate Specificity of the Integral Membrane Protease OmpT Determined by Spatially Addressed Peptide Libraries
AUTHOR(S): Dekker, Niek; Cox, Ruud C.; Kramer, R. Arjen; Egmond, Maarten R.
CORPORATE SOURCE: Department of Enzymology and Protein Engineering, Centre for Biomembranes and Lipid Enzymology, Institute of Biomembranes, Utrecht University, Utrecht, 3584 CH, Neth.
SOURCE: Biochemistry (2001), 40(6), 1694-1701
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Escherichia coli outer membrane protease T (OmpT) is an endopeptidase that specifically cleaves between two consecutive basic residues. In this study we have investigated the substrate specificity of OmpT using spatially addressed SPOT peptide libraries. The peptide acetyl-Dap(dnp)-Ala-Arg↓Arg-Ala-Lys(Abz)-Gly was synthesized directly onto cellulose membrane. The peptide contained the aminobenzoyl (Abz) fluorophore, which was internally quenched by the dinitrophenyl (dnp) moiety. Treatment of the SPOT membrane with the small, water-soluble protease trypsin resulted in highly fluorescent peptide SPOTs. However, no peptide cleavage was observed after incubation with detergent-solubilized OmpT, a macromol. complex with an estimated mol. mass of 180 kDa. This problem could be solved by the introduction of a long, polar polyoxyethylene glycol linker between the membrane support and the peptide. Peptide libraries for the P2, P1, P1', and P2' positions in the substrate were screened with OmpT, and peptides of pos. SPOTs were resynthesized and subjected to kinetic measurements in solution The best substrate Abz-Ala-Lys-Lys-Ala-Dap(dnp)-Gly had a turnover number kcat of 40 s-1, which is 12-fold higher than the starting substrate. Peptides containing an acidic residue at P2 or P2' were not substrates for OmpT, suggesting that long-range electrostatic interactions are important for the formation of the enzyme-substrate complex. OmpT was highly selective toward L-amino acids at P1 but was less so at P1' where a peptide with D-Arg at P1' was a competitive inhibitor (Ki of 19 μM). An affinity chromatog. resin based on these findings was developed, which allowed for the one-step purification of OmpT from a bacterial lysate. The implications of the determined consensus substrate sequence (Arg/Lys)↓(Arg/Lys)-Ala for the proposed biol. function of OmpT in defense against antimicrobial peptides are discussed.

IT **330651-45-1**
RL: PRP (Properties)
(SPOT peptide libraries utilizing PEG linker permit anal. of substrate specificity for Escherichia coli outer membrane protease OmpT)

RN 330651-45-1 HCAPLUS
CN Glycine, N2-(2-aminobenzoyl)-L-arginyl-L-arginyl-3-[(2,4-dinitrophenyl)amino]-L-alanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:197496 HCAPLUS
DOCUMENT NUMBER: 131:29254
TITLE: Interdependency of Sequence and Positional Specificities for Cysteine Proteases of the Papain Family
AUTHOR(S): Naegler, Dorit K.; Tam, Wendy; Storer, Andrew C.; Krupa, Joanne C.; Mort, John S.; Menard, Robert
CORPORATE SOURCE: Biotechnology Research Institute, National Research Council of Canada, Montreal, QC, H4P2R2, Can.
SOURCE: Biochemistry (1999), 38(15), 4868-4874
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The specificity of cysteine proteases is characterized by the nature of the amino acid sequence recognized by the enzymes (sequence specificity) as well as by the position of the scissile peptide bond (positional specificity, i.e., endopeptidase, aminopeptidase, or carboxypeptidase). In this paper, the interdependency of sequence and positional specificities for selected members of this class of enzymes has been investigated using fluorogenic substrates where both the position of the cleavable peptide bond and the nature of the sequence of residues in P2-P1 are varied. The results show that cathepsins K and L and papain, typically considered to act strictly as endopeptidases, can also display dipeptidyl carboxypeptidase activity against the substrate Abz-FRF(4NO2)A and dipeptidyl aminopeptidase activity against FR-MCA. In some cases the activity is even equal to or greater than that observed with cathepsin B and DPP-I (dipeptidyl peptidase I), which have been characterized previously as exopeptidases. In contrast, the exopeptidase activities of cathepsins K and L and papain are extremely low when the P2-P1 residues are A-A, indicating that, as observed for the normal endopeptidase activity, the exopeptidase activities rely heavily on interactions in subsite S2 (and possibly S1). However, cathepsin B and DPP-I are able to hydrolyze substrates through the exopeptidase route even in absence of preferred interactions in subsites S2 and S1. This is attributed to the presence in cathepsin B and DPP-I of specific structural elements which serve as an anchor for the C- or N-terminus of a substrate, thereby allowing favorable enzyme-substrate interaction independently of the P2-P1 sequence. As a consequence, the nature of the residue at position P2 of a substrate, which is usually the main factor determining the specificity for cysteine

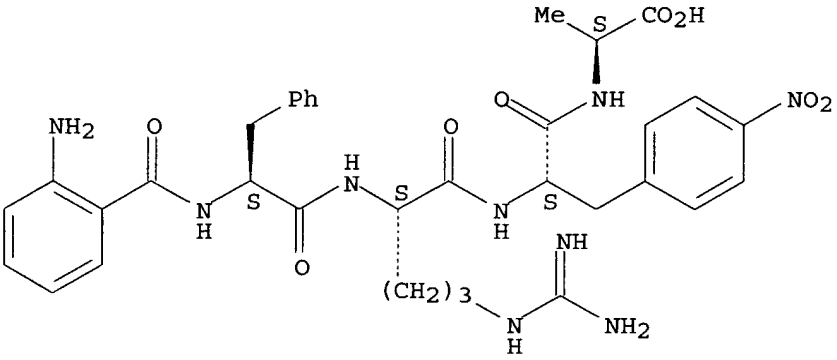
proteases of the papain family, does not have the same contribution for the exopeptidase activities of cathepsin B and DPP-I.

IT **227029-48-3**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interdependency of sequence and positional specificities for cysteine proteases of papain family)

RN 227029-48-3 HCAPLUS

CN L-Alanine, N-(2-aminobenzoyl)-L-phenylalanyl-L-arginyl-4-nitro-L-phenylalanyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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L12 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:77586 HCAPLUS
DOCUMENT NUMBER: 130:139657
TITLE: Preparation of modified nociceptin analogs for treatment of vasomotor disturbances
INVENTOR(S): Thogersen, Henning; Madsen, Kjeld; Olsen, Uffe Bang; Johansen, Nils Langeland; Scheideler, Mark
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9903880	A1	19990128	WO 1998-DK326	19980713
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9883342	A1	19990210	AU 1998-83342	19980713
US 5998375	A	19991207	US 1998-115209	19980714
PRIORITY APPLN. INFO.:			DK 1997-867 A	19970715

US 1997-52862P P 19970717
WO 1998-DK326 W 19980713

OTHER SOURCE(S): MARPAT 130:139657

AB The present invention relates to novel peptides (X)n-A1-A2-A3-A4-A5-A6-A7-A8-A9-A10-A11-A12-A13-A14-A15-A16-A17-(Y)m-A18 [A1 = bond, optionally acylated small or lipophilic amino acid; A2 = optionally acylated aromatic, lipophilic, or small amino acid; A2-A3 = 5-aminopentanoic acid, N-methylanthranilic acid, 4-aminocyclohexanecarboxylic acid, 3-(aminomethyl)benzoic acid; A4 = small or aromatic amino acid; A3-A4 = N-methylanthranilic acid; A5 = lipophilic amino acid; A6, A7 = independently small, polar, or lipophilic amino acid; A8 = polar amino acid, L-Ala, D-Ala; A9, A10, A11, A12, A13, A14, A15 = independently lipophilic or polar amino acid; A16, A17= independently bond, small or polar amino acid; A18 = OH, NH2; X, Y = independently polar, lipophilic, aromatic, or small amino acid; n + m = 0-82; two or more of A1 to A17, X, and Y may independently form a bridge such as a disulfide bridge, lactam bridge, or Gly-lactam bridge; with the proviso that there are at least wo simultaneous amino acid modifications relative to the nociceptin sequence or an unnatural amino acid in position A1], pharmaceutically acceptable salts thereof, pharmaceutical compns. containing them, methods for preparing the compds., use of the compds. for preparing medicaments for treating vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes, and to a method of treating vasomotor disturbances.

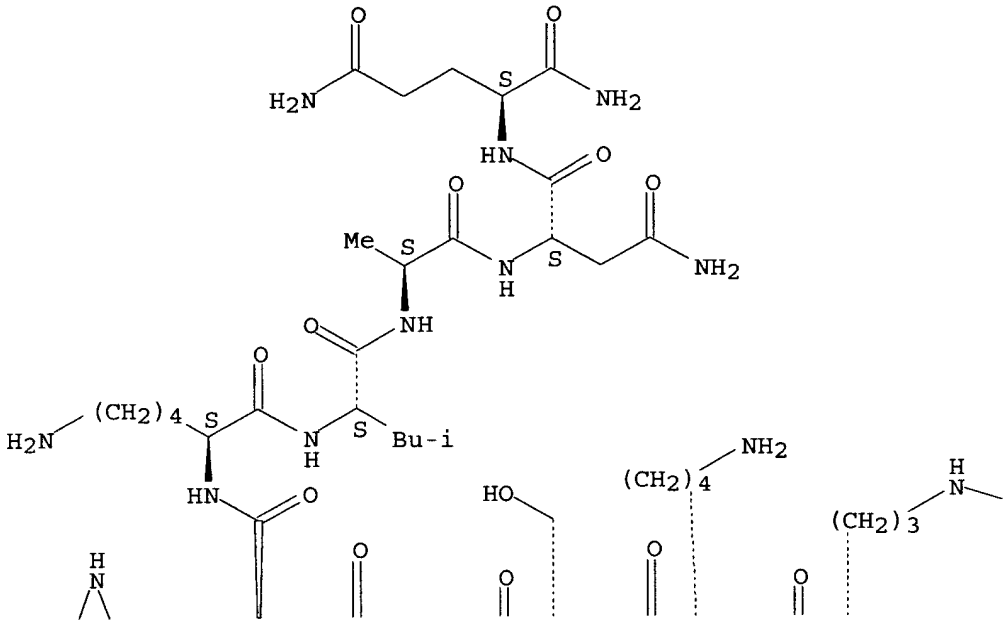
IT **220045-54-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of modified nociceptin analogs for treatment of vasomotor disturbances)

RN 220045-54-5 HCAPLUS

CN Orphanin FQ (swine), 7-L-aspartic acid-11-(N5-glycyl-L-ornithine)-17-L-glutamamide-, (7→11)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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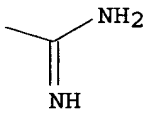

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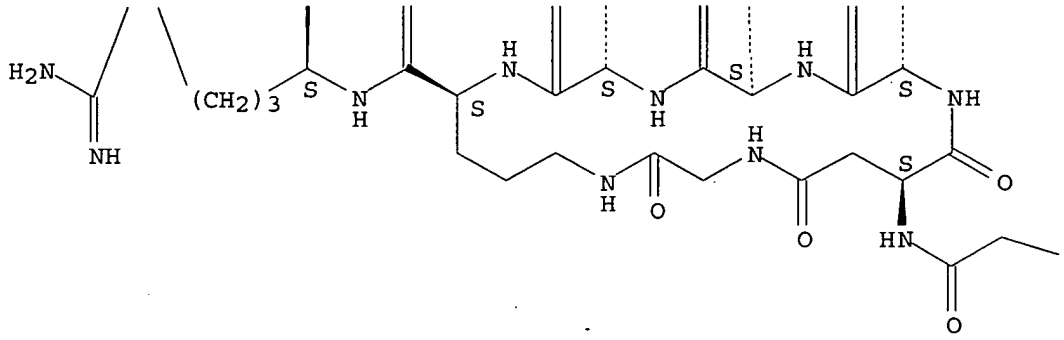

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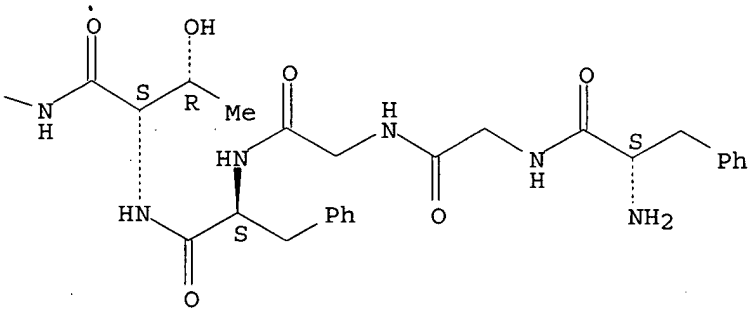

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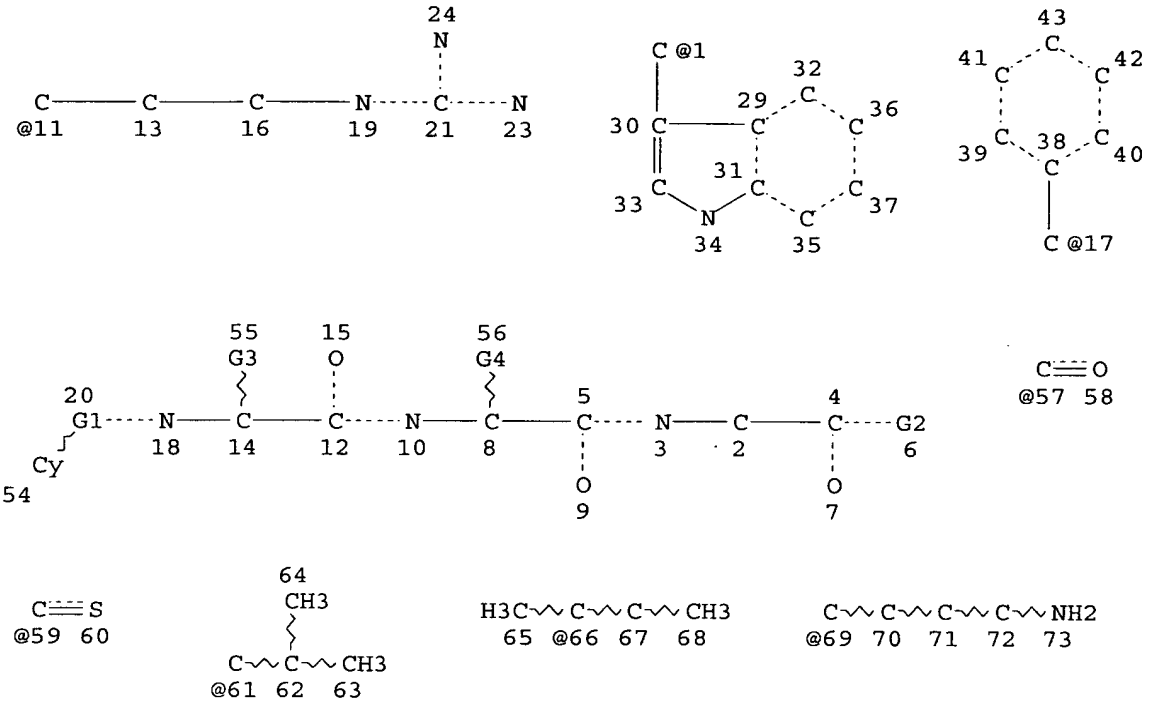

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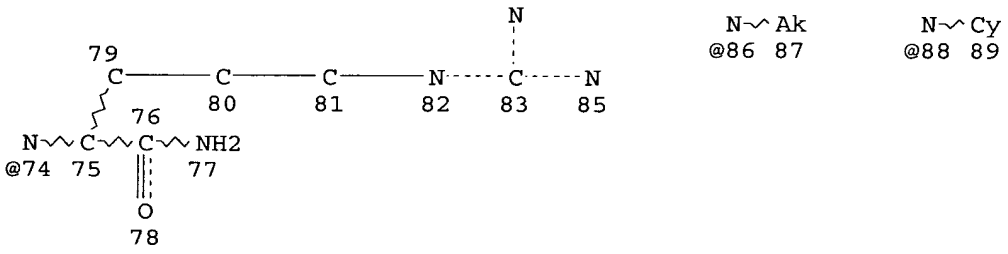

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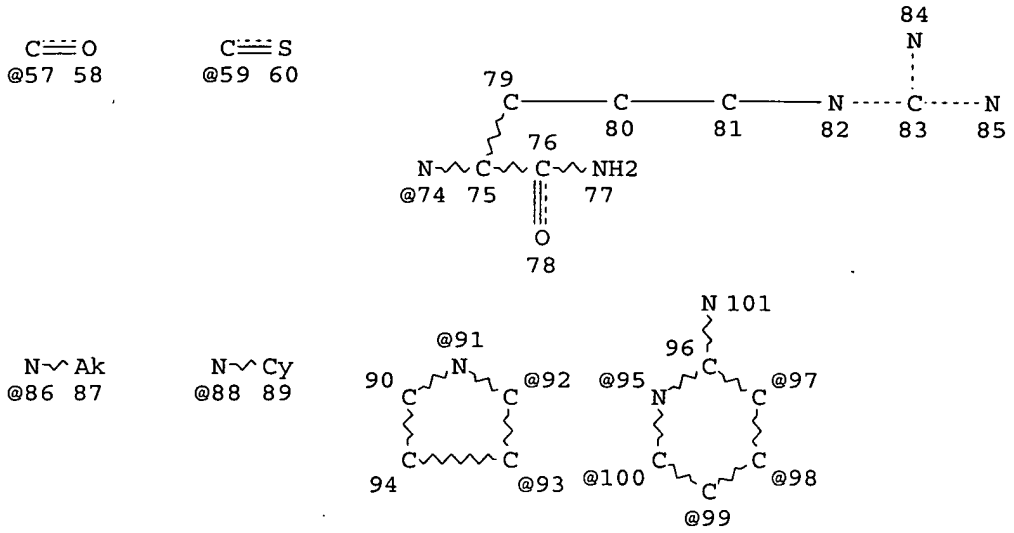

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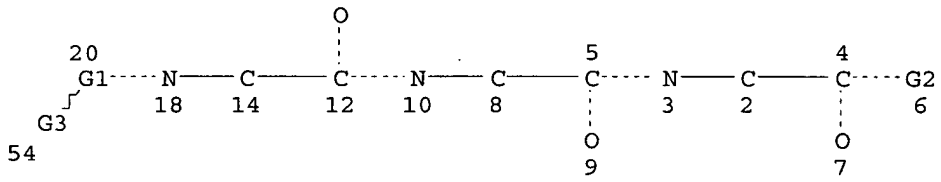

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L19  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:739844  HCAPLUS
TITLE:                    Structure-based design of serine protease inhibitors:
                          Discovery of selective chymase inhibitors containing a
                          novel β-amidophosphonic acid recognition motif
AUTHOR(S):                Hawkins, Michael J.; Greco, M. N.; Powell,
                          E. T.; Corcoran, T. W.; De Garavilla, L.; Kauffman, J.
                          A.; Wang, Y.; Minor, L.; Di Cera, E.; Sukumar, N.;
                          Chen, Z-W.; Pineda, A. O.; Mathews, F. S.;
                          Maryanoff, B. E.
CORPORATE SOURCE:         Drug Discovery, Johnson & Johnson Pharmaceutical
                          Research & Development, Spring House, PA, 19477, USA
SOURCE:                   Abstracts of Papers, 230th ACS National Meeting,
                          Washington, DC, United States, Aug. 28-Sept. 1, 2005
                          (2005), MEDI-336.  American Chemical Society:
                          Washington, D. C.
                          CODEN: 69HFCL
DOCUMENT TYPE:            Conference; Meeting Abstract; (computer optical disk)
LANGUAGE:                 English
AB   Human chymase, a chymotrypsin-like serine protease present in the mast
     cell and released on activation, has been implicated in various pathol.
     conditions associated with inflammation, including airway inflammation.  We
     identified β-amidophosphonic acid 1 as a selective inhibitor of
     chymase (IC50 = 0.2 μM) through routine screening.  We solved the X-ray
     crystal structure of 2-chymase and used the information in a
     structure-based optimization protocol.  Details of the interactions of 2
     within the active site of chymase will be discussed.  Compound 2 was
     efficacious in the standard sheep model of asthma.  Further optimization of 2
     led to a series of potent, selective, orally active chymase inhibitors,
     represented by 3, from which we identified a suitable compound for preclin.
     development.  Details of these studies will be presented.

L19  ANSWER 2 OF 11  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2005:732638  HCAPLUS
DOCUMENT NUMBER:          143:212017
TITLE:                    Preparation of phosphorus containing compounds as
                          novel inhibitors of chymase
INVENTOR(S):              Hawkins, Michael J.; Greco, Michael N.;
                          Powell, Eugene; De Garavilla, Lawrence;
                          Maryanoff, Bruce E.
PATENT ASSIGNEE(S):       Janssen Pharmaceutica, N. V., Belg.
SOURCE:                   PCT Int. Appl., 199 pp.
                          CODEN: PIXXD2
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DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005073214	A2	20050811	WO 2005-US1659	20050118
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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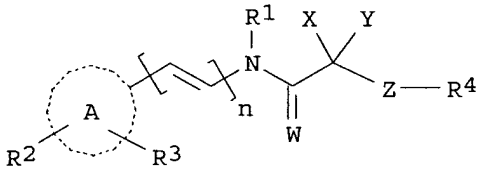
US 2005176769	A1	20050811	US 2005-37938	20050118

PRIORITY APPLN. INFO.: US 2004-538663P P 20040123
OTHER SOURCE(S): MARPAT 143:212017
GI



I

AB The present invention is directed to phosphorus containing compds. I (circle A = aryl, hetroaryl, benzo fused heterocyclyl, cyclopropyl when n is 0 and one of R2 or R3 = Ph, and benzo fused cycloalkyl, and ring A is optionally substituted with R2 and R3; R2 = C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C1-6 alkylthio, OCF3, NH2, etc.; R3 = C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C1-6 alkoxy, C1-6 alkylthio, OCF3, OCH2(C2-6)alkenyl, NH2, NH(C1-6)alkyl, etc.; R4 = C1-6 alkyl, C1-6 alkenyl, C1-6 alkoxy, C1-6 alkylthio, aryl(C1-6)alkyl, aryl(C2-6)alkenyl, halo, C(:O)Cy, organoamido, aryl, etc.; n = 0, 1; W = O, S; X = H, C1-3 alkyl; Y = C1-6 alkyl substituted with aminosulfonyl or hydroxy, SO3H, CO2H, heteroaryl, organophosphonyl, etc.), methods for preparing these compds., compns., intermediates and derivs. thereof, and methods for treating inflammatory and serine protease mediated disorders.

L19 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:658188 HCAPLUS
TITLE: Structure-based design of serine protease inhibitors: Discovery of cathepsin G and chymase inhibitors containing a novel β-ketophosphonic acid motif
AUTHOR(S): Greco, Michael N.; **Hawkins, Michael J.**; Powell, Eugene T.; Almond, Harold A.; Corcoran, Thomas; de Garavilla, Lawrence; Kauffman, Jack A.; Recacha, Rosario; Chattopadhyay, Debashish; Andrade-Gordon, Patricia; Giardino, Edward;

Maryanoff, Bruce E.
CORPORATE SOURCE: Drug Discovery, Johnson and Johnson Pharmaceutical Research and Development, Spring House, PA, 19477, USA
SOURCE: Abstracts of Papers, 228th ACS National Meeting, Philadelphia, PA, United States, August 22-26, 2004 (2004), MEDI-326. American Chemical Society: Washington, D. C.
CODEN: 69FTZ8
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Cathepsin (Cat G), a chymotrypsin-like serine protease that is stored in the azurophilic granules of neutrophils and released on activation, has been implicated in various pathol. conditions associated with inflammation, including chronic pulmonary diseases. We identified β-keto phosphonic acid 1 as a moderate inhibitor of Cat G (IC50 = 4.1 μM) by high-throughput screening. We solved the X-ray crystal structure of 1-Cat G and used the information in a structure-based optimization protocol, which led to 2 (IC50 = 38 nM). In further enzymic profiling, 2 was found to be a potent inhibitor of chymase (IC50 =2 nM), a chymotrypsin-like serine protease in mast cells that is released on activation and has also been implicated in inflammatory diseases. Studies with dual protease inhibitor 2 in animal models of inflammation have delivered pos. findings, particularly with respect to airway inflammation and neutrophil influx. Details on the interactions of 2 within the active sites of Cat G and chymase will be discussed.

L19 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:462860 HCAPLUS
DOCUMENT NUMBER: 141:33797
TITLE: Substituted heterocyclic acyl-tripeptides useful as thrombin receptor modulators
INVENTOR(S): **McComsey, David F.; Maryanoff, Bruce E.; Hawkins, Michael J.**
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 444,327, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6747127	B1	20040608	US 2000-565715	20000505
TR 200102502	T2	20020521	TR 2001-200102502	19991119
US 2004063903	A1	20040401	US 2003-606422	20030626
PRIORITY APPLN. INFO.:			US 1998-112313P P	19981214
			US 1999-444327 B2	19991119
			US 2000-565715 A3	20000505

OTHER SOURCE(S): MARPAT 141:33797
AB Substituted heterocyclic acyl-tripeptides, useful as thrombin receptor modulators, are disclosed, as is their use in wound healing and preventing platelet aggregation. Pharmaceutical compns. comprising the substituted heterocyclic acyl-tripeptides of the invention, as well as methods of treating conditions mediated by the thrombin receptor, are also disclosed.
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:696543 HCAPLUS
DOCUMENT NUMBER: 139:230617
TITLE: Preparation of [[N-(styrylsulfonyl)pyrrolidinyl]carbamoyl]phenylguanidines and analogs as serine protease inhibitors
INVENTOR(S): Greco, Michael N.; **Maryanoff, Bruce E.**; **Hawkins, Michael J.**; Boyd, Robert E.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Ser. No. 90,872.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003166681	A1	20030904	US 2002-303230	20021125
US 6710061	B2	20040323		
US 2003004186	A1	20030102	US 2002-90872	20020305
US 6538017	B2	20030325		
US 2003166680	A1	20030904	US 2002-303229	20021125
US 6630505	B2	20031007		
US 2003203936	A1	20031030	US 2003-439884	20030516
US 6890939	B2	20050510		

PRIORITY APPLN. INFO.: US 2001-274845P P 20010309
US 2002-90872 A2 20020305
US 2002-303230 A3 20021125
OTHER SOURCE(S): MARPAT 139:230617
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I and II; R1 = H, alkyl, cycloalkyl, etc.; R2 = H, OH, alkoxy, etc.; R3 = aryl, arylalkyl, heteroarylalkyl, etc.; G = H, halo, OH, etc.; n = 1-2], useful as a serine protease or dual-serine protease inhibitors, particularly, as Factor Xa or tryptase inhibitors, were prepared E.g., a multi-step synthesis of III (starting from 3-aminopyrrolidine and Me 4-formylbenzoate) which showed Ki of 0.2 μM against Factor Xa, was given.

L19 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:335110 HCAPLUS
DOCUMENT NUMBER: 138:338296
TITLE: Preparation of phosphonic acid compounds as inhibitors of serine proteases
INVENTOR(S): Greco, Michael N.; Almond, Harold R.; De Garavilla, Lawrence; **Hawkins, Michael J.**; **Maryanoff, Bruce E.**; Qian, Yun; Walker, Donald Gilmore; Cesco-Cancian, Sergio; Nilsen, Christopher Norman; Patel, Mitul N.; Humora, Michael J.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035654	A1	20030501	WO 2002-US33206	20021017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2464111	AA	20030501	CA 2002-2464111	20021017
EP 1438316	A1	20040721	EP 2002-802153	20021017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002013961	A	20040831	BR 2002-13961	20021017
JP 2005537217	T2	20051208	JP 2003-538169	20021017
NO 2004002057	A	20040518	NO 2004-2057	20040518

PRIORITY APPLN. INFO.:	US 2001-330343P	P	20011019
	WO 2002-US33206	W	20021017

OTHER SOURCE(S): CASREACT 138:338296; MARPAT 138:338296
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

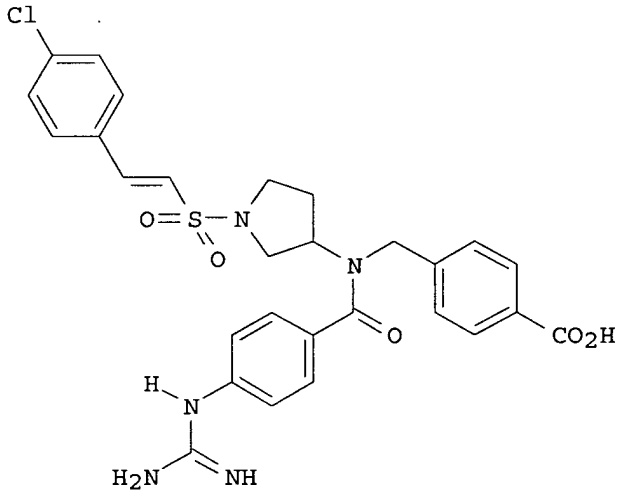
AB Phosphonic acid compds. [I; wherein R1 = (substituted) heterocyclic ring with the point of attachment being a nitrogen ring atom, amino; R2, R3, independently = H, (C1-C4)alkyl, (C1-C4)alkoxy, (C2-C4)alkenyl, amino, halo, hydroxy, or R2 and R3 together form at least one ring fused to the benzene ring; R4 = (C1-C4)alkyl, aryl, heteroaryl; R5 = H, (C1-C8)alkyl; R6 = (C1-C8)alkyl, aryl(C1-C8)alkyl, (C1-C8)alkoxy, aryl(C1-C8)alkoxy, (C2-C8)alkenyloxy, etc.; X, Y, independently = H, (C1-C8)alkyl, (C1-C8)alkoxy, (C2-C8)alkenyloxy, cycloalkyl, heterocyclyl, aryl, aryloxy, etc.; Z = a bond, H, (C1-C8)alkyl] were prepared For example, compound (II) was prepared in several steps. The prepared compds. are useful as serine protease inhibitors and, thus, are useful for treating inflammatory and serine protease mediated disorders. For example, compound II showed good inhibition against cathepsin G (IC50 = .081 μM).
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:754354 HCAPLUS
DOCUMENT NUMBER: 137:262949
TITLE: Preparation of [[N-(styrylsulfonyl)pyrrolidinyl]carbamoyl]phenylguanidines and analogs as serine protease inhibitors
INVENTOR(S): Greco, Michael N.; **Maryanoff, Bruce E.**; **Hawkins, Michael J.**; Boyd, Robert E.
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002076945	A1	20021003	WO 2002-US6475		20020305
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2440389	AA	20021003	CA 2002-2440389		20020305
EP 1385822	A1	20040204	EP 2002-739093		20020305
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004520438	T2	20040708	JP 2002-576206		20020305
PRIORITY APPLN. INFO.:			US 2001-274845P	P	20010309
			WO 2002-US6475	W	20020305

OTHER SOURCE(S): MARPAT 137:262949
GI



III

AB H2NC(:NH)NHZCOZ1Z2SO2R3 [I; R3 = (un)substituted (hetero)aryl[alk(en)yl]; Z = (un)substituted 1,4-phenylene; Z1 = NR1 and Z2 = 3,1-(oxo)azacycloalkylene or Z1 = 1,3-(oxo)azacycloalkylene and z2 = NR1; R1 = H, alkyl, (hetero)aryl[alk(en)yl], etc.] were prepared Thus, pyrrolidine-3-amine was condensed with 4-(OHC)C6H4CO2Me and the N-protected product reduced to yield, after deprotection, HZ2NRCH2C6H4(CO2Me)-4 (Z2 = pyrrolidine-1,3-diyl)(II; R = H) which was N-acylated by 4-(O2N)C6H4COCl to give II [R = COC6H4(NO2)-4]. The latter was N-sulfonylated by 4-ClC6H4CH:CHSO2Cl to give, in 4 addnl. steps, title compound III. Data for biol. activity of I were given.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:207068 HCAPLUS
DOCUMENT NUMBER: 136:395323
TITLE: Nonpeptide Inhibitors of Cathepsin G: Optimization of a Novel β-Ketophosphonic Acid Lead by Structure-Based Drug Design
AUTHOR(S): Greco, Michael N.; **Hawkins, Michael J.**; Powell, Eugene T.; Almond, Harold R., Jr.; Corcoran, Thomas W.; de Garavilla, Lawrence; Kauffman, Jack A.; Recacha, Rosario; Chattopadhyay, Debashish; Andrade-Gordon, Patricia; **Maryanoff, Bruce E.**
CORPORATE SOURCE: Johnson Johnson Pharmaceutical Research & Development, Spring House, PA, 19477-0776, USA
SOURCE: Journal of the American Chemical Society (2002), 124(15), 3810-3811
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:395323
AB The serine protease cathepsin G (EC 3.4.21.20; Cat G), which is stored in the azurophilic granules of neutrophils (polymorphonuclear leukocytes) and released on degranulation, has been implicated in various pathol. conditions associated with inflammation. By employing high-throughput screening, we identified a β-ketophosphonic acid as a moderate inhibitor of Cat G (IC50 = 4.1 μM). We were fortunate to obtain a co-crystal of the same with Cat G and solve its structure by x-ray crystallog. (3.5 Å). Structural details from the x-ray anal. of the ligand bound Cat G served as a platform for optimization of this lead compound by structure-based drug design. With the aid of mol. modeling, substituents were attached to the 3-position of the 2-naphthyl ring of the β-ketophosphonic acid, which occupies the S1 pocket of Cat G, to provide an extension into the hydrophobic S3 region. Thus, we arrived at an analog with an 80-fold potency improvement over the parent (IC50 = 53 nM). From these results, it is evident that the β-ketophosphonic acid unit can form the basis for a novel class of serine protease inhibitors.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:421161 HCAPLUS
DOCUMENT NUMBER: 133:53708
TITLE: Substituted heterocyclic acyl-tripeptides useful as thrombin receptor modulators
INVENTOR(S): **McComsey, David F.; Maryanoff, Bruce E.; Hawkins, Michael J.**
PATENT ASSIGNEE(S): Ortho-McNeil Pharmaceutical, Inc., USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035942	A1	20000622	WO 1999-US27570	19991119

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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CA 2355818	AA	20000622	CA 1999-2355818		19991119
EP 1140985	A1	20011010	EP 1999-961738		19991119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
BR 9916811	A	20020115	BR 1999-16811		19991119
TR 200102502	T2	20020521	TR 2001-200102502		19991119
AU 771844	B2	20040401	AU 2000-18256		19991119
NO 2001002939	A	20010809	NO 2001-2939		20010614
PRIORITY APPLN. INFO.:			US 1998-112313P	P	19981214
			US 1999-444327	A	19991119
			WO 1999-US27570	W	19991119

OTHER SOURCE(S): MARPAT 133:53708

AB Substituted heterocyclic acyl-tripeptides, useful as thrombin receptor modulators, are disclosed, as is their use in wound healing and preventing platelet aggregation. Pharmaceutical compns. comprising the substituted heterocyclic acyl-tripeptides of the invention, as well as methods of treating conditions mediated by the thrombin receptor, are also disclosed.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:348254 HCAPLUS
DOCUMENT NUMBER: 131:102532
TITLE: Heterocycle-peptide hybrid compounds. Aminotriazole-containing agonists of the thrombin receptor (PAR-1)
AUTHOR(S): **McComsey, David F.**; **Hawkins, Michael J.**; Andrade-Gordon, Patricia; Addo, Michael F.; Oksenberg, Donna; **Maryanoff, Bruce E.**
CORPORATE SOURCE: Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1999), 9(10), 1423-1428
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

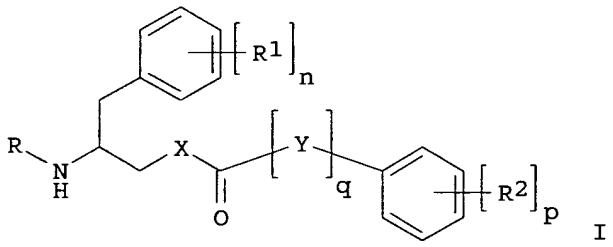
AB The thrombin receptor PAR-1 is activated by α-thrombin to stimulate cells, including platelets, through the tethered-ligand sequence SFLLRN. The authors have discovered a novel series of heterocycle-peptide hybrids comprised of a tripeptide segments, such as Cha-Arg-Phe (Cha = cyclohexylalanine), and an N-terminal heterocyclic group, many of which behave as full PAR-1 agonists. Certain compds. with an aminotriazole group, such as RCO-Cha-Arg-Phe-NH2 (R = 5-amino-1,2,4-triazole-3-yl) and RCO-Phe-Arg-Phe-NH2 (R = 5-amino-1,2,4-triazole-3-yl), are nearly as potent as SFLLRN-NH2 in inducing platelet aggregation. Also, some arylethenoyl "N-capped" compds., such as RCO-Cha-Arg-Phe-NH2 [R = 5-(o-chlorocinnamido)-1,2,4-triazol-3-yl; 5-(2-thienyl)acrylamido-1,2,4-triazol-3-yl], exhibit mixed PAR-1 agonist-antagonist activity.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:268479 HCAPLUS
DOCUMENT NUMBER: 128:321928
TITLE: Preparation of phenylalaninol derivatives for the treatment of central nervous system disorders
INVENTOR(S): Dax, Scott L.; Greco, Michael N.; **Hawkins, Michael J.**; **Maryanoff, Bruce E.**; McNally, James; Vavouyios-Smith, Anna
PATENT ASSIGNEE(S): Ortho Pharmaceutical Corp., USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9817636	A1	19980430	WO 1997-US18683	19971020
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9746747	A1	19980515	AU 1997-46747	19971020
PRIORITY APPLN. INFO.:			US 1996-29583P P	19961022
			WO 1997-US18683 W	19971020

OTHER SOURCE(S): MARPAT 128:321928
GI



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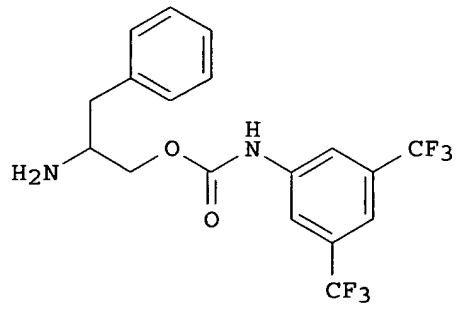

II

AB The title compds. [I; R = H, C1-8 alkyl, C3-8 cycloalkyl, etc.; R1 = H, C1-5 alkyl, C1-5 alkoxy, etc.; R2 = H, C1-5 alkyl, C1-5 alkoxy, etc.; n = 1-5; X = O, NH; Y = NH, CH2; q = 0-1] and their salts which are modulators of the NPY1 receptor and display anxiolytic animal models, and are therefore useful in the treatment of anxiety, convulsions, sleeplessness, muscle spasm, and benzodiazepine drug overdose, were prepared Thus, reaction of N-(tert-butoxycarbonyl)-D-phenylalaninol with 3,5-bis(trifluoromethyl)phenyl isocyanate in dichloroethane followed by treatment of the resulting O-[N-3,5-bis(trifluoromethyl)phenyl]carbamoyl-N-(tert-butoxycarbonyl)-D-phenylalaninol with CF3COOH in dichloroethane afforded the title compound (R)-II.CF3COOH which showed IC50 of 1.0 μM against NPY binding and IC50 of 30.0 μM against the binding of porcine PYY.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L6         12249 SEA FILE=REGISTRY SSS FUL L4
L7              STR
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L9            85 SEA FILE=REGISTRY ABB=ON  PLU=ON  L8 AND SQL=<4
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L11           13 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 AND PD=<DECEMBER 15, 1998

L12           27 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L10 NOT L11
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                 BRUCE ELIOT"/AU)
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                 ("HAWKINS MICHAEL J"/AU OR "HAWKINS MICHAEL JOHN"/AU) OR
                 HAWKINS M/AU OR HAWKINS M J/AU
L16            3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L13 AND L14 AND L15) NOT
                 (L11 OR L12)
L18           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND L15
L19           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L16 OR L18
L20         5474 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6
L21            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ((L13 OR L14 OR L15) AND L20)
                 NOT (L11 OR L12 OR L19)
L22          251 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L13 OR L14 OR L15) AND
                 PD=<DECEMBER 14, 1998
L23           20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L22 AND THROMBIN
L24           20 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L21 OR L23) NOT (L11 OR L12
                 OR L19)


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=> d ibib abs hitstr l24 1-20

L24  ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        1998:637324  HCAPLUS
DOCUMENT NUMBER:         130:34770
TITLE:                   Macrocyclic inhibitors of serine proteases
AUTHOR(S):               Greco, Michael N.; Maryanoff, Bruce E.
```

CORPORATE SOURCE: Drug Discovery The R.W. Johnson Pharmaceutical Research Institute, Spring House, PA, USA
SOURCE: Advances in Amino Acid Mimetics and Peptidomimetics (**1997**), 1, 41-76
CODEN: AAAMF9
PUBLISHER: JAI Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

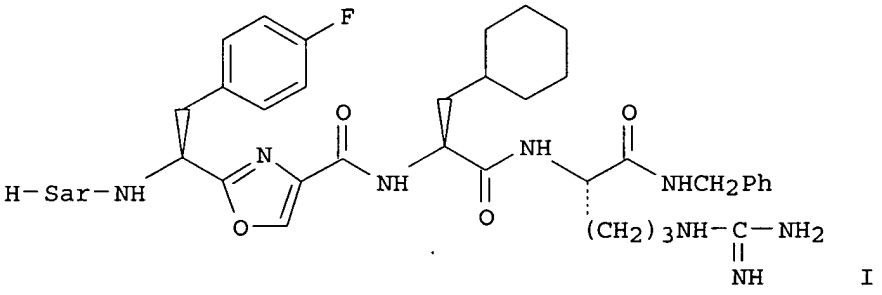
AB A review with .apprx.119 refs. Macrocyclic peptides play an important role in many biol. processes. In comparison to their acyclic counterparts, the restricted conformational flexibility of macrocyclic peptides offers potential advantages for binding interactions with bioreceptors. For example, Nature employs macrocyclic peptide hormones such as oxytocin, the vasopressins, and somatostatin to regulate such critical processes as lactation, uterine contraction, vasoconstriction, and growth hormone release. The serpin superfamily is a unique class of inhibitor proteins that regulate the actions of serine proteases, proteolytic enzymes involved in the regulation of physiol. events such as blood coagulation, fibrinolysis, connective tissue turnover, inflammatory responses, and complement activation. Serpins operate by a mechanism whereby they present a peptide recognition epitope as a part of macrocyclic array, or loop of the enzyme. The macrocyclic peptide motif has been under-explored as a means to discover novel serine protease inhibitors. In this chapter, we review serine protease inhibitors from the perspective of our studies involving the macrocyclic peptide cyclotheonamide A (CtA), a marine natural product. CtA, itself, is a very potent inhibitor of trypsin and a potent inhibitor of **thrombin.** We outline our progression from fundamental studies of CtA to a focused drug discovery approach aimed at identifying novel inhibitors of **thrombin**, a serine protease that plays a central role in the control of thrombosis and hemostasis. Our protein structure-based approach utilized X-ray and NMR structural information to design hybrid structures that combined elements of CtA and the **thrombin** -recognition tripeptide, D-Phe-Pro-Arg, in an analogy with fibrinogen Aα-chain motifs. We describe synthetic chemical, enzyme inhibition, and mol. modeling, and then rationalize **thrombin** vs. trypsin inhibition by considering features of the CtA-bound X-ray structures of each enzyme. Our approach resulted in a class of novel macrocyclic inhibitors of **thrombin** and trypsin with good in vitro potency. Although enzyme selectivity for **thrombin** over trypsin was unexceptional, we managed to find some selective inhibitors of trypsin.

REFERENCE COUNT: 118 THERE ARE 118 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:529507 HCAPLUS
TITLE: In-depth study of tripeptide-based acylheterocycles as inhibitors of **thrombin.** Effective utilization of the S1' subsite and its implications to protein structure-based drug design.
AUTHOR(S): **Maryanoff, Bruce E.**; Hecker, L. R.; Schott, M. R.; Yabut, S. C.; Zhang, H. -C.; Andrade-Gordon, P.; Giardino, E. C.; Kauffman, J. A.; Lewis, J. M.; Costanzo, Michael J.
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (**1998**), MEDI-021. American Chemical Society: Washington, D. C.

CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB We have briefly described (J. Med. Chemical 1996, 39, 3039) a series of potent α- **thrombin** inhibitors based on the motif Me-(D-Phe)-Pro-Arg-Het and found the preferred form of "Het" to be 2-benzothiazolyl (1) (Ki = 0.19 nM). Although 1 has good selectivity for **thrombin** over other key coagulation enzymes, it caused severe hypotension at about 5 times the efficacious dose. We have since identified other inhibitors from our series which have good in vitro potency with a much improved side effect profile. The design, synthesis, and extensive structure-activity relationships (SAR) of this series will be presented.

L24 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:482687 HCAPLUS
DOCUMENT NUMBER: 129:231006
TITLE: **Thrombin** receptor (PAR-1) antagonists. Heterocycle-based peptidomimetics of the SFLLR agonist motif
AUTHOR(S): Hoekstra, William J.; Hulshizer, Becky L.; **Mccomsey, David F.**; Andrade-Gordon, Patricia; Kauffman, Jack A.; Addo, Michael F.; Oksenberg, Donna; Scarborough, Robert M.; **Maryanoff, Bruce E.**
CORPORATE SOURCE: The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1998**), 8(13), 1649-1654
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB The **thrombin** receptor (PAR-1) is activated by α- **thrombin** to stimulate various cell types, including platelets, through the tethered-ligand sequence SFLLRN. A series of oxazole- or thiazole-based carboxamides, designed after SFLLR, were synthesized and evaluated in vitro. The compds. inhibited platelet aggregation induced by SFLLRN-NH2 or α- **thrombin**, and blocked the binding of [3H]-Ser-(p-F-Phe)-Har-Leu-Har-Lys-Tyr-NH2 (Har = homoarginine) to a CHRF membrane preparation of PAR-1. Oxazole-based peptide I bound to PAR-1 with an IC50 of 1.6 μM, and gave IC50 values of 25 μM and 6.6 μM against α- **thrombin**- and SFLLRN-NH2-induced platelet aggregation,

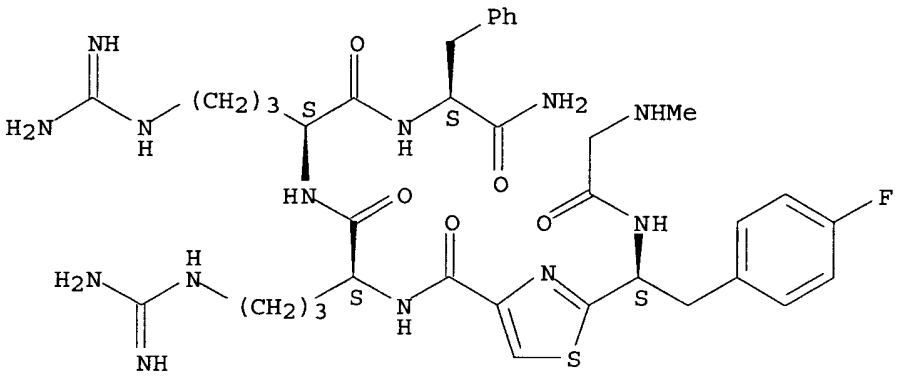
resp.

IT **212756-53-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of oxazole- and thiazole-based peptidomimetics as **thrombin** receptor antagonists)

RN 212756-53-1 HCAPLUS

CN L-Phenylalaninamide, N-methylglycyl-2-[(1S)-1-amino-2-(4-fluorophenyl)ethyl]-4-thiazolecarbonyl-L-arginyl-L-arginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:805968 HCAPLUS

DOCUMENT NUMBER: 128:3874

TITLE: Solid-Phase Synthesis of Arginine-Containing Peptides by Guanidine Attachment to a Sulfonyl Linker

AUTHOR(S): Zhong, H. Marlon; Greco, Michael N.; **Maryanoff, Bruce E.**

CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA

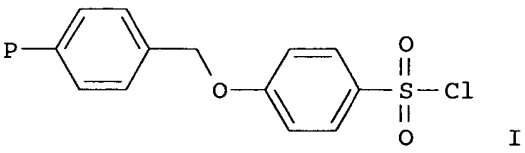
SOURCE: Journal of Organic Chemistry (**1997**), 62(26), 9326-9330
CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



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AB In the area of mol. diversity generation, the authors have developed a new arenesulfonyl linker for the solid-phase organic synthesis of compds. containing

guanidine groups (viz. I; P = polystyrene resin). In the cases examined for illustration, the Arg guanidine group was attached to the novel solid support via a SO2-N bond, followed by subsequent chemical manipulation and release of the product from the resin. This new resin, I, bearing an electron-rich arenesulfonyl group, has a reasonable loading capacity of ca. 0.5 mmol/g, is stable to various reaction conditions, and is compatible with both tert-butoxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) peptide chemical Three model arginine-containing peptides were synthesized by appending amino acids onto a resin-bound arginine derivative at either or both termini: H-Arg-Phe-OH, H-Phe-Arg-Ala-OMe, and H-Phe-Gly-Arg-Ala-OMe, obtained in isolated, purified yields of 72%, 50%, and 40%, resp. Furthermore, the authors applied resin I to the synthesis of H-Ser-Phe-Leu-Leu-Arg-Asn-NH2, an agonist hexapeptide for the **thrombin** receptor (16% yield).

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:568161 HCAPLUS
DOCUMENT NUMBER: 127:234616
TITLE: Macrocyclic peptides useful in the treatment of **thrombin** related disorders
INVENTOR(S): Greco, Michael N.; **Maryanoff, Bruce E.**
PATENT ASSIGNEE(S): Ortho Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE	
WO 9730080	A1	19970821	WO 1997-US2575		19970219	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM						
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG						
US 5888971	A	19990330	US 1996-603666		19960220	
CA 2246811	AA	19970821	CA 1997-2246811		19970219	<--
AU 9720526	A1	19970902	AU 1997-20526		19970219	<--
AU 717024	B2	20000316				
ZA 9701419	A	19980819	ZA 1997-1419		19970219	<--
EP 932619	A1	19990804	EP 1997-908677		19970219	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI						
NZ 331447	A	20000228	NZ 1997-331447		19970219	
JP 2000504728	T2	20000418	JP 1997-529578		19970219	
NZ 501877	A	20010223	NZ 1997-501877		19970219	
TW 517062	B	20030111	TW 1997-86103657		19970324	
NO 9803800	A	19981019	NO 1998-3800		19980819	<--
PRIORITY APPLN. INFO.:			US 1996-603666	A	19960220	
			WO 1997-US2575	W	19970219	

OTHER SOURCE(S): MARPAT 127:234616
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [m = 2-12; B = (CR5R6NHCHR4)b where CR5R6 is bound to the ring methylene and the CHR4 is bound to A; G = (CHR7ER8R9NH)g where NH is bound to the ring methylene and CHR7 is bound to the amido group; E = C(CH2)q, where q = 0-12; a, b, g = 0 or 1; R3 = H, OH, C1-5 alkoxy; n = 1 or 2; R4, R7 = H, C1-5 alkyl, carboxyC1-5 alkyl, (un)substituted phenyl; R5, R6 = H, or form a carbonyl group with the carbon of attachment; R8, R9 = H, or form a carbonyl group with the carbon of E] and II [W = N, S, O; same m, A, B, and G] or their pharmaceutically acceptable salts, were prepared as **thrombin** and trypsin inhibitors. Thus, macrocyclic peptide III was prepared by a multistep procedure and tested in vitro for inhibition of human α- **thrombin** (Ki = 0.0031±0.0008 μM) and trypsin (Ki = 0.004±0.0018 μM). Prepared agents I and II inhibited **thrombin** at nanomolar levels and exhibit reasonable selectivity for **thrombin** over trypsin.

L24 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:162122 HCAPLUS
TITLE: Design of macrocyclic **thrombin** inhibitors.
AUTHOR(S): Greco, Michael N.; Powell, Eugene T.; Hecker, Leonard R.; Andrade-Gordon, Patricia; Kauffman, Jack A.; Lewis, Joan M.; Venkatapathy, Ganesh; Tulinsky, Alexander; **Maryanoff, Bruce E.**
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Book of Abstracts, 213th ACS National Meeting, San Francisco, April 13-17 (**1997**), MEDI-290. American Chemical Society: Washington, D. C. CODEN: 64AOAA
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Since **thrombin** is a trypsin-like serine protease with a central role in the bioregulation of thrombosis and hemostasis, selective active-site-directed inhibitors represent potentially useful therapeutic agents for the management of thrombotic disorders. By following a protein structure-based protocol, we have designed potent, macrocyclic active-site inhibitors of **thrombin.** We plan to discuss structure-function issues relating ring size and P3/P1' modifications to enzyme inhibition. Chemical synthesis, in vitro biochem. evaluation, and details of the X-ray crystal structure of a complex between 1 and **thrombin** will also be presented.

L24 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:142079 HCAPLUS
DOCUMENT NUMBER: 126:248109
TITLE: NMR three-dimensional solution structure of the serine protease inhibitor cyclotheonamide A
AUTHOR(S): McDonnell, Patricia A.; Caldwell, Gary W.; Leo, Gregory C.; Podlogar, Brent L.; **Maryanoff, Bruce E.**
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Biopolymers (**1997**), 41(3), 349-358 CODEN: BIPMAA; ISSN: 0006-3525
PUBLISHER: Wiley

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The NMR solution conformation of cyclotheonamide A (CtA) was determined in aqueous media. The data produced 15 distance and 10 torsional constraints which were used to generate conformations using restrained simulated annealing (SA) and distance geometry/simulated annealing (DG/SA) calcns. Two different calcn. protocols were performed to ensure proper sampling of conformational space and even though the torsional restraints were input differently, both calcn. methods yielded the same conformation of CtA. In the structure calcns., all solns. of the Karplus equation were sampled simultaneously using the restrained SA protocol and large ranges were used for the dihedral restraints in the DG/SA protocol because all solns. to Karplus equation could not be sampled simultaneously. The solution conformation was also compared to the solid state x-ray conformations of CtA bound to **thrombin** and trypsin. The conformation of the residues important for active site binding (D-Phe, h-Arg, and Pro) are nearly identical in aqueous solution and solid state with largest differences at the a-Ala and v-Tyr residues. CtA appears to be pre-ordered in structure and does not undergo a significant conformational change upon binding to the enzyme active site.

L24 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:124457 HCAPLUS
DOCUMENT NUMBER: 126:131784
TITLE: Preparation of peptidyl heterocycles useful in the treatment of **thrombin** related disorders
INVENTOR(S): Costanzo, Michael J.; **Maryanoff, Bruce E.**
PATENT ASSIGNEE(S): Ortho Pharmaceutical Corp., USA
SOURCE: PCT Int. Appl., 133 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9640742	A1	19961219	WO 1996-US8430		19960603 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN					
US 5827860	A	19981027	US 1995-481934		19950607 <--
AU 9658867	A1	19961230	AU 1996-58867		19960603 <--
ZA 9604761	A	19971205	ZA 1996-4761		19960606 <--
TW 474936	B	20020201	TW 1996-85108207		19960708
PRIORITY APPLN. INFO.:			US 1995-481934	A	19950607
			WO 1996-US8430	W	19960603

OTHER SOURCE(S): MARPAT 126:131784
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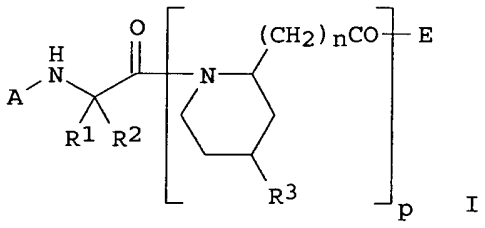

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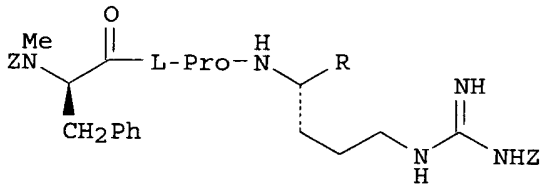

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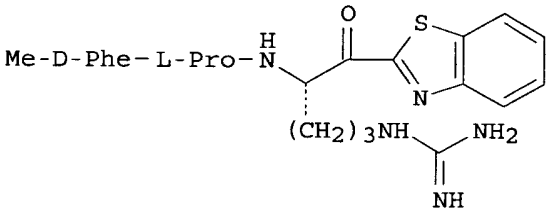

III

AB Peptidyl heterocycles I [A = C1-8 alkyl, carboxy-C1-4 alkyl, C1-4 alkoxycarbonyl-C1-4 alkyl, (un)substituted phenyl-C1-4 alkyl, N-substituted D- or L-amino acid, N-substituted D- and/or L-amino acid-containing dipeptide; R1 = H, C1-5 alkyl; R2 = amino-C2-5 alkyl, guanidino-C2-5 alkyl, C1-4 alkylguanidino-C2-5 alkyl, di-C1-4 alkylguanidino-C2-5 alkyl, amidino-C2-5 alkyl, C1-4 alkylamidino-C2-5 alkyl, di-C1-4 alkylamidino-C2-5 alkyl, C1-3 alkoxy-C2-5alkyl, (un)substituted phenyl; R3 = H, C1-5 alkyl; n = 0-3; p = 0, 1; E = heterocycle] and their pharmaceutically acceptable salts are compds. useful in the treatment of **thrombin** and trypsin related disorders. Thus, condensation of protected arginine aldehyde tripeptide II (Z = PhCH2O2C; R = CHO) with acetone cyanohydrin gave tripeptide cyanohydrin II [R = CH(OH)CN], which underwent methanolysis in the presence of HCl to give imidate salt II [R = CH(OH)C(OMe):NH.HCl], followed by cyclocondensation with 2-aminothiophenol to give benzothiazole derivative II [R = CH(OH)Q; Q = 2-benzothiazolyl]. Oxidation of II [R = CH(OH)Q] with Dess-Martin periodinane and deprotection gave the desired **thrombin** inhibitor III. III inhibited **thrombin** with Ki = 0.00023 μM in an in vitro assay.

L24 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1997:121405 HCAPLUS
DOCUMENT NUMBER:	126:131785
TITLE:	Preparation of peptidyl heterocycles useful in the treatment of **thrombin** related disorders
INVENTOR(S):	Costanzo, Michael J.; **Maryanoff, Bruce E.**
PATENT ASSIGNEE(S):	Ortho Pharmaceutical Corp., USA
SOURCE:	PCT Int. Appl., 134 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640741	A1	19961219	WO 1996-US8360	19960602 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
US 5827866	A	19981027	US 1995-482587	19950607 <--
AU 9659678	A1	19961230	AU 1996-59678	19960602 <--
ZA 9604762	A	19971208	ZA 1996-4762	19960606 <--
TW 567187	B	20031221	TW 1996-85108211	19960708
PRIORITY APPLN. INFO.:			US 1995-482587 A	19950607
			WO 1996-US8360 W	19960602

OTHER SOURCE(S): MARPAT 126:131785
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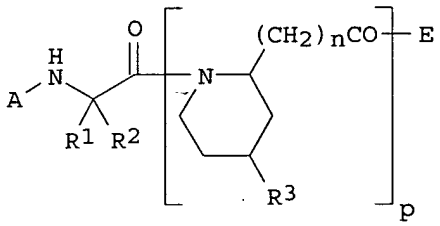

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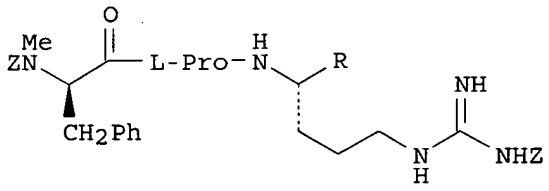

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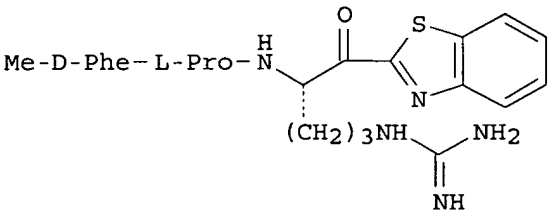
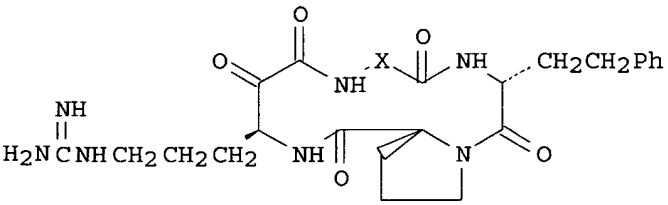


III

AB Peptidyl heterocycles I [A = C1-8 alkyl, carboxy-C1-4 alkyl, C1-4 alkoxycarbonyl-C1-4 alkyl, (un)substituted phenyl-C1-4 alkyl, N-substituted D- or L-amino acid, N-substituted D- and/or L-amino acid-containing dipeptide; R1 = H, C1-5 alkyl; R2 = amino-C2-5 alkyl, guanidino-C2-5 alkyl, C1-4 alkylguanidino-C2-5 alkyl, di-C1-4 alkylguanidino-C2-5 alkyl, amidino-C2-5 alkyl, C1-4 alkylamidino-C2-5 alkyl, di-C1-4 alkylamidino-C2-5 alkyl, C1-3 alkoxy-C2-5alkyl, (un)substituted phenyl; R3 = H, C1-5 alkyl; n = 0-3; p = 0, 1; E = heterocycle] and their pharmaceutically acceptable salts are compds. useful in the treatment of **thrombin** and trypsin related disorders. Thus, condensation of protected arginine aldehyde tripeptide

II (Z = PhCH2O2C; R = CHO) with acetone cyanohydrin gave tripeptide cyanohydrin II [R = CH(OH)CN], which underwent methanolysis in the presence of HCl to give imidate salt II [R = CH(OH)C(OMe):NH.HCl], followed by cyclocondensation with 2-aminothiophenol to give benzothiazole derivative II [R = CH(OH)Q; Q = 2-benzothiazolyl]. Oxidation of II [R = CH(OH)Q] with Dess-Martin periodinane and deprotection gave the desired **thrombin** inhibitor III. III inhibited **thrombin** with Ki = 0.00023 μM in an in vitro assay.

L24 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:49331 HCAPLUS
DOCUMENT NUMBER: 126:171871
TITLE: Novel **thrombin** inhibitors that are based on a macrocyclic tripeptide motif
AUTHOR(S): Greco, Michael N.; Powell, Eugene T.; Hecker, Leonard R.; Andrade-Gordon, Patricia; Kauffman, Jack A.; Lewis, Joan M.; Ganesh, Venkatapathy; Tulinsky, Alexnder; **Maryanoff, Bruce E.**
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (**1996**), 6(24), 2947-2952
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A series of macrocyclic α-keto amides containing the D-Phe-Pro-Arg (fPR) motif were synthesized and evaluated in vitro as inhibitors of human α- **thrombin** and bovine trypsin. Structure-function studies, relating ring size and modifications at the P3 and P1' positions to enzyme inhibition, are described. An X-ray crystallog. study was performed on a ternary complex formed form I [X = (CH2)7], **thrombin**, and hirugen.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:675375 HCAPLUS
DOCUMENT NUMBER: 126:154368
TITLE: Crystal structures of **thrombin** with thiazole-containing inhibitors: probes of the S1' binding site
AUTHOR(S): Matthews, John H.; Krishnan, R.; Costanzo, Michael J.; **Maryanoff, Bruce E.**; Tulinsky, A.
CORPORATE SOURCE: Dep. Chem., Michigan State Univ., East Lansing, MI, 48824, USA

SOURCE: Biophysical Journal (**1996**), 71(5), 2830-2839
CODEN: BIOJAU; ISSN: 0006-3495
PUBLISHER: Biophysical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Structures of human **thrombin** complexed with hirugen and 2 active site inhibitors, RWJ-50353 (N-methyl-D-phenylalanyl-N-[5-[(aminoiminomethyl)amino]-1-[[(2-benzothiazolyl)carbonyl]butyl]-L-prolinamide trifluoroacetate hydrate) and RWJ-50215 (N-[4-(aminoiminomethyl)amino]-1-[2-(thiazol-2-ylcarbonylethyl)piperidin-1-ylcarbonyl]butyl]-5-(dimethylamino)naphthalenesulfonamide trifluoroacetate hydrate), were determined by x-ray crystallog. The refinements converged at R values of 0.158 in the 7.0-2.3-Å range for RWJ-50353 and 0.155 in the 7.0-1.8-Å range for RWJ-50215. Interactions between the protein and the thiazole rings of the 2 inhibitors provided new valuable information about the S1' binding site of **thrombin.** The RWJ-50353 inhibitor consisted of an S1'-binding benzothiazole group linked to the D-Phe-Pro-Arg chloromethyl ketone motif. Interactions with the S1-S3 sites were similar to the D-phenylalanyl-propyl-arginyl chloromethylketone structure. In RWJ-50215, a S1'-binding 2-ketothiazole group was added to the **thrombin** inhibitor-like framework of dansylarginine N-(3-ethyl-1,5-pentanediyl)amine. The geometry at the S1-S3 sites here was also similar to that of the parent compound The benzothiazole and 2-ketothiazole groups. bound in a cavity surrounded by His-57, Try-60A, Trp-60D, and Lys-60F. This location of the S1' binding site was consistent with previous structures of **thrombin** complexes with hirulog-3, CVS-995, and hirutonin-2 and -6. The ring N atom of the RWJ-50353 benzothiazole moiety formed a H-bond with His-57, and Lys-60F reoriented because of close contacts. The O and N atoms of the ketothiazole moiety of RWJ-50215 H-bonded with the NZ atom of Lys-60F.

L24 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1996:422519 HCAPLUS
DOCUMENT NUMBER: 125:104245
TITLE: Potent **thrombin** inhibitors that probe the S1' subsite: tripeptide transition state analogs based on a heterocycle-activated carbonyl group
AUTHOR(S): Costanzo, Michael J.; **Maryanoff, Bruce**; Hecker, Leonard R.; Schott, Mary R.; Yabut, Stephen C.; Zhang, Han-Cheng; Andrade-Gordon, Patricia; Kauffman, Jack A.; Lewis, Joan M.; et al.
CORPORATE SOURCE: R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Journal of Medicinal Chemistry (**1996**), 39(16), 3039-3043
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of peptidoyl heterocycles with the motif Me-(D-Phe)-Pro-Arg-Het was synthesized and evaluated for inhibition of human α-**thrombin** and bovine trypsin. The preferred form of "Het" was a 2-azole, with the best **thrombin** inhibitor (Ki = 0.19 nM) having a 2-benzothiazole group (2, RWJ-50353). The best selectivity for **thrombin** over trypsin (try/thr ratio = 88) was obtained with the N-methyl-2-imidazole group (**thrombin** Ki = 50 nM). In analogs of 2 with the activated carbonyl reduced to an alc. group (two diastereomers), there was a substantial loss of **thrombin** inhibition , as expected for a transition state analog. Inhibitor 2 shows excellent selectivity for **thrombin** over other blood coagulation

enzymes, such as plasmin (ratio = 12,000), tPA (ratio = 3,300), activated protein C (ratio = 19,000), and streptokinase (ratio = 6,300), but the selectivity of 2 for **thrombin** over trypsin is more modest (ratio = 16). Compound 2 has an IC50 value of 23±2 nM for inhibition of **thrombin**-induced platelet aggregation (human, gel-filtered). The mol. structure of a complex between 2, human α- **thrombin**, and hirugen was determined by x-ray crystallog. Besides the standard active-site interactions for tripeptide **thrombin** inhibitors, the structure shows novel interactions in the S1' region, where the benzothiazole ring forms a hydrogen bond with His-57 and an aromatic stacking interaction with Trp-60D of the unique insertion loop of **thrombin.**

L24 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:392102 HCAPLUS
DOCUMENT NUMBER: 125:143319
TITLE: Peptidyl heterocycles useful in the treatment of **thrombin** related disorders
INVENTOR(S): Costanzo, Michael J.; **Maryanoff, Bruce E.**
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 59 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5523308	A	19960604	US 1995-486473	19950607 <--
CA 2224110	AA	19961219	CA 1996-2224110	19960603 <--
WO 9640748	A1	19961219	WO 1996-US8456	19960603 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN				
AU 9659713	A1	19961230	AU 1996-59713	19960603 <--
AU 721079	B2	20000622		
EP 833839	A1	19980408	EP 1996-917014	19960603 <--
EP 833839	B1	20030108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
CN 1192747	A	19980909	CN 1996-196103	19960603 <--
JP 11506762	T2	19990615	JP 1997-501056	19960603
RU 2181125	C2	20020410	RU 1998-100420	19960603
AT 230757	E	20030115	AT 1996-917014	19960603
PL 184986	B1	20030131	PL 1996-323825	19960603
ES 2191102	T3	20030901	ES 1996-917014	19960603
IL 122436	A1	20040620	IL 1996-122436	19960603
ZA 9604759	A	19971208	ZA 1996-4759	19960606 <--
TW 470751	B	20020101	TW 1996-85108206	19960708
NO 9705747	A	19980203	NO 1997-5747	19971205 <--

PRIORITY APPLN. INFO.: US 1995-486473 A 19950607
WO 1996-US8456 W 19960603

OTHER SOURCE(S): MARPAT 125:143319

AB Peptidyl heterocycles ANHCR1R2CO[B(CH2)nCO]pE (A = alkyl, substituted phenylalkyl, amino acid moiety, etc.; R1 = H, alkyl; R2 = aminoalkyl, alkoxyalkyl, Ph or substituted phenyl; B = 1,2-piperidinediyl or

4-alkyl-1,2-piperidinediyl, n = 0-3; p = 0, 1; E = heterocyclyl) or their pharmaceutically acceptable salts were prepared for use in the treatment of **thrombin** and trypsin related disorders. Thus, N-methyl-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1S-[(benzothiazol-2-yl)carbonyl]butyl]-L-prolinamide (1) was prepared from N-CBZ-N-methyl-D-phenylalanyl-L-prolyl-NG-CBZ-L-arginine-aldehyde by sequential reaction with acetone cyanohydrin, gaseous HCl in MeOH, 2-aminothiophenol, and Dess-Martin periodinane. Compound 1 and 56 other synthesized compds. were tested for their ability to inhibit **thrombin** or trypsin mediated hydrolysis. Thr IC50 (μM) and Trp IC50 (μM) values for compound 1 are 0.00023 and 0.0031, resp.

L24 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:333128 HCAPLUS
DOCUMENT NUMBER: 125:115113
TITLE: Transformation of the marine natural product cyclotheonamide A by aqueous base. X-Ray analysis of a novel ligand complexed with human α-**thrombin**
AUTHOR(S): **Maryanoff, Bruce E.**; Zhang, Han-Cheng; Greco, Michael N.; Zhang, Erli; Vanderhoff-Hanaver, Peggy; Tulinsky, Alexander
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Res. Inst., Spring House, PA, 19477, USA
SOURCE: Tetrahedron Letters (**1996**), 37(21), 3667-3670
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treatment of the macrocyclic pentapeptide cyclotheonamide A with aqueous sodium carbonate or triethylamine at 23° generated two isomeric products. X-ray anal. of a complex with α- **thrombin** indicates a ring-opened pentapeptide from cleavage at the α-keto amide bond. However, mass spectral data and a model study suggest a different product.

L24 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:924639 HCAPLUS
TITLE: Macrocyclic peptide inhibitors of human α-**thrombin**: Cyclotheonamide and its analogs.
AUTHOR(S): **Maryanoff, Bruce E.**; Greco, Michael N.; Zhang, Han-Cheng; Glover, Karen A.; Kauffman, Jack A.; Andrade-Gordon, Patricia; Tulinsky, Alexander
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharmaceutical Research Institute, PA, 19477, USA
SOURCE: Book of Abstracts, 210th ACS National Meeting, Chicago, IL, August 20-24 (**1995**), Issue Pt. 2, ORGN-025. American Chemical Society: Washington, D. C.
CODEN: 61XGAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB By means of structure-based drug discovery, we have pursued novel inhibitors of human α- **thrombin**, a serine protease central to the bioregulation of thrombosis and hemostasis. Cyclotheonamide A (CtA), a marine sponge natural product that represents a novel class of macrocyclic inhibitors, served as a prototype for drug design. We characterized the interactions of CtA within the active site of **thrombin** by X-ray crystallog. and developed synthetic methodol. to

prepare CtA and its analogs by a convergent route involving [2 + 3] segment condensation. Diverse analogs were obtained and evaluated for **thrombin** inhibition. Other aspects of **thrombin** inhibitors, especially those with a macrocyclic peptide structure, will be discussed.

L24 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:777430 HCAPLUS
DOCUMENT NUMBER: 123:329242
TITLE: Cyclotheonamide derivatives: synthesis and **thrombin** inhibition. Exploration of specific structure-function issues
AUTHOR(S): **Maryanoff, Bruce E.**; Zhang, Han-Cheng; Greco, Michael N.; Glover, Karen A.; Kauffman, Jack A.; Andrade-Gordon, Patricia
CORPORATE SOURCE: Drug Discovery, R. W. Johnson Pharm. Res. Inst., Spring House, PA, 19477, USA
SOURCE: Bioorganic & Medicinal Chemistry (**1995**), 3(8), 1025-38
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Macrocyclic pentapeptide analogs of the sponge natural product cyclotheonamide A (CtA, -3) were prepared by the authors convergent synthetic protocol, in which a late-stage primary amine group is available for substitution (Maryanoff et al. Proc Natl. Acad. Sci. U.S.A. 1993, 90, 8048). These analogs, as well as CtA and cyclotheonamide B (CtB), were examined for their ability to inhibit the serine protease α-**thrombin**, in comparison with suitable reference stds. The authors characterized Michaelis-Menten and slow-binding kinetics for the cyclotheonamide derivs. An attempt was made to utilize the unoccupied hydrophobic S3 subsite of **thrombin**. Also, removal of the hydroxyphenyl group, which is thought to be involved in an aromatic stacking interaction with Trp60D of **thrombin**, was explored. The importance of the α-keto and olefin groups was examined The relation of structure and function with the analogs proved to be less predictable than anticipated.

L24 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:553946 HCAPLUS
DOCUMENT NUMBER: 123:228873
TITLE: Macrocyclic Peptide Inhibitors of Serine Proteases. Convergent Total Synthesis of Cyclotheonamides A and B via a Late-Stage Primary Amine Intermediate. Study of **Thrombin** Inhibition under Diverse Conditions. [Erratum to document cited in CA122:161323]
AUTHOR(S): **Maryanoff, Bruce E.**; Greco, Michael N.; Zhang, Han-Cheng; Andrade-Gordon, Patricia; Kauffman, Jack A.; Nicolaou, K. C.; Liu, Aijun; Brungs, Peter H.
CORPORATE SOURCE: R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Journal of the American Chemical Society (**1995**), 117(19), 5427
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The errors were not reflected in the abstract or the index entries.

L24 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:319903 HCAPLUS
DOCUMENT NUMBER: 122:161323
TITLE: Macrocyclic Peptide Inhibitors of Serine Proteases. Convergent Total Synthesis of Cyclotheonamides A and B via a Late-Stage Primary Amine Intermediate. Study of **Thrombin** Inhibition under Diverse Conditions
AUTHOR(S): **Maryanoff, Bruce E.**; Greco, Michael N.; Zhang, Han-Cheng; Andrade-Gordon, Patricia; Kauffman, Jack A.; Nicolaou, K. C.; Liu, Aijun; Brungs, Peter H.
CORPORATE SOURCE: R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SOURCE: Journal of the American Chemical Society (**1995**), 117(4), 1225-39
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 122:161323
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Cyclotheonamide A (I; R = CHO) (II), a cyclic pentapeptide isolated from the marine sponge Theonella sp., is an inhibitor of serine proteases such as α- **thrombin** and trypsin. The total synthesis of II by a convergent [3 + 2] fragment-condensation route is described in detail. The requisite protected amino acid starting materials were processed and converted into two segments, III (TBS = Me3CSiMe2, PhtN = phthalimido) and IV (Fmoc = 9-fluorenylmethoxycarbonyl, Ts = tosyl), which were coupled with BOP reagent in 75% yield to give a pentapeptide intermediate. After selective removal of the terminal protecting groups, the critical macrocyclization was effected with BOP-Cl in 65% yield under high-dilution conditions to provide V in 25% overall yield. Macrocycle V was then processed in four steps to II, which was isolated and purified by HPLC (trifluoroacetate salt). Synthetic II was identical to the natural product by 500 MHz 1H NMR, 100-MHz 13C NMR, HPLC, TLC, fast-atom-bombardment mass spectrometry, optical rotation, and bioassay. The 13C NMR spectrum of II in D2O shows virtually exclusive population by the hydrated form of the α-keto amide (gem-diol structure). Cyclotheonamide B (I; R = Ac) was also prepared through an analogous transformation. This chemical protocol offers a useful vehicle for the systematic preparation of cyclotheonamide analogs, and because of a the late-stage primary amine intermediate, analogs with a modified N-acyl or N-alkyl substituent should be conveniently accessible. This seems important for satisfying the hydrophobic S3 binding pocket of **thrombin** which is vacant for the CtA-**thrombin** complex but effectively utilized by the standard D-Phe-Pro-Arg tripeptide inhibitors. Other chemical highlights of the synthesis include (1) homologation of protected arginal via a cyanohydrin to obtain the homoarginine subunit, (2) use throughout of a monoprotected guanidine, and (3) macrocyclic lactam formation with an unprotected hydroxyl substituent. The characteristics of II as a **thrombin** inhibitor were also examined Either competitive, Michaelis-Menten kinetics or slow, tight-binding kinetics were observed, depending on the substrate, the **thrombin** concentration, and the order of addition of components. Given sufficient time for

equilibration of II and **thrombin**, slow-binding inhibition is generally displayed.

L24 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:23073 HCAPLUS
DOCUMENT NUMBER: 120:23073
TITLE: Molecular basis for the inhibition of human α-**thrombin** by the macrocyclic peptide cyclotheonamide A
AUTHOR(S): **Maryanoff, Bruce E.**; Qiu, Xiayang; Padmanabhan, K. P.; Tulinsky, Alexander; Almond, Harold R., Jr.; Andrade-Gordon, Patricia; Greco, Michael N.; Kauffman, Jack A.; Nicolaou, K. C.; et al.
CORPORATE SOURCE: Drug Discovery Div., R. W. Johnson Pharm. Res. Inst., Spring House, PA, 19477, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1993**), 90(17), 8048-52
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The macrocyclic peptide cyclotheonamide A (CtA), isolated from the marine sponge Theonella, represents an unusual class of serine protease inhibitors. A complex of this inhibitor with human α-**thrombin**, a protease central to the bioregulation of thrombosis and hemostasis, was studied by x-ray crystallog. This work (2.3-Å resolution) confirms the structure of CtA and reveals intimate details about its mol. recognition within the enzyme active site. Interactions due to the "Pro-Arg motif" (Arg occupancy of the S1 specificity pocket; formation of a hydrogen-bonded 2-strand antiparallel B-sheet with Ser214-Gly216) and the α-keto amide group of CtA are primarily responsible for binding to **thrombin**, with the α-keto amide serving as a transition-state analog. A special interaction with the "insertion loop" of **thrombin** (Tyr60A-Thr60I) is manifested through engagement of the hydroxyphenyl group of CtA with Trp60D as part of an "aromatic stacking chain.". Biochem. inhibition data (Ki values at 37°) were obtained for CtA with **thrombin** and a diverse collection of serine proteases. Thus, CtA is just a moderate inhibitor of human α-**thrombin** (Ki = 0.18 μM) but a potent inhibitor of trypsin (Ki = 0.023 μM) and streptokinase (K1 = 0.035 μM). The relative lack of potency of CtA as a **thrombin** inhibitor is discussed with respect to certain structural features of the enzyme complex. The authors also report the total synthesis of CtA, by a convergent [2 + 3] fragment-condensation approach, to serve the preparation of cyclotheonamide analogs for structure-function studies.

L24 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:47826 HCAPLUS
DOCUMENT NUMBER: 106:47826
TITLE: Inhibition of protein cross-linking in calcium-enriched human erythrocytes and activated platelets
AUTHOR(S): Lorand, L.; Barnes, N.; Bruner-Lorand, J. A.; **Hawkins, M.**; Michalska, M.
CORPORATE SOURCE: Dep. Biochem., Mol. Biol. Cell Biol., Northwestern Univ., Evanston, IL, 60201, USA
SOURCE: Biochemistry (**1987**), 26(1), 308-13
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treatment of human erythrocytes with Ca2+, in the presence of ionophore A 23187, caused the formation of high-mol.-weight (>106) membrane protein polymers. This phenomenon, known to involve crosslinking of essentially all of the band 4.1 and 2.1 (ankyrin) proteins, as well as some spectrin, band 3, and Hb mols., could be prevented by preincubating the cells with a noncompetitive inhibitor of intrinsic transglutaminase, 2-[3-(diallylamino)propionyl]benzothiophene (I), at concns. of about (3-6) + 10-4M. I also eliminated the proteolytic breakdown of the 2 major transmembrane proteins, band 3 and glycophorin, which would otherwise occur during the Ca2+ loading of fresh human red cells. In addition, I effectively blocked the formation of a crosslinked protein polymer in **thrombin**-activated human platelets.

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